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| In re U.S. Patent Application of | ) |
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| Harold M. Bates | ) |
| | ) |
| Serial No.: Filed concurrently herewith | ) Examiner: [not yet assigned] |
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| Filed: Filed concurrently herewith | ) Group: [not yet assigned] |
| | ) |
| For: DETECTION OF ASYMPTOMATIC CORONARY ARTERY DISEASE USING ATHEROGENIC PROTEINS AND ACUTE PHASE REACTANTS | ) |

INFORMATION DISCLOSURE STATEMENT

Mail Stop Patent Application
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Applicant wishes to make of record the following documents (clean copies and 18 Forms PTO-1449 listing them are enclosed). Neither this Information Disclosure Statement nor its filing constitutes either an admission that any of the documents is prior art or a representation that a search has been made.

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## REMARKS

The relevance of these documents is set forth in the application. Additional comments concerning them are set forth below.

1. U. S. Patent No. 5,024,829 (Berger et al.) concerns a method of imaging coronary thrombi using monoclonal antibodies. "Coronary thrombosis plays a major role in clinical instability and development of myocardial infarction in patients with angina" (column 1, lines 7-9).

2. U. S. Patent No. 5,026,537 (Daddona et al.) concerns a method of imaging atherosclerotic plaque using radiolabeled monoclonal antibodies that are specific for activated platelets or activated endothelial cells.

3. U. S. Patent No. 5,046,499 (Berger) concerns a method for myocardial infarct risk assessment. Figure 5 is an ROC curve (analysis), showing the diagnostic performance of antimyosin relating to the incidence of true positives to false positives.

4. U. S. Patent No. 5,120,834 (Gargan et al.) concerns fibrin-specific monoclonal antibodies.

5. U. S. Patent No. 5,196,324 (Bumol et al.) concerns a naturally occurring, minimally modified LDL antigen which is present in atherosclerotic lesions as well as in the

serum of a high percentage of patients with coronary artery disease. It also concerns antibodies, including monoclonal antibodies, to that antigen and methods for using the antibodies in the diagnosis and treatment of atherosclerotic disease. "As modified LDLs are the progenitors of foam cell formation leading to atherosclerotic plaques, the ability to detect modified LDL in serum or plasma provides a diagnostic tool to assess plaque body burden, new plaque formation, to aid in risk assessment in asymptomatic patients or in the management of therapy" (column 6, lines 19-24).

6. U. S. Patent No. 5,223,410 (Gargan et al.) concerns the production of monoclonal antibodies, including to fibrin.

7. U. S. Patent No. 5,362,649 (Schwertner) concerns a method for determining the likelihood that a patient is at risk for coronary artery disease involving measuring the patient's serum cholesterol concentration of fatty acids and derivatives.

8. U. S. Patent No. 5,380,667 (Schwertner) concerns a method for predicting the risk of coronary artery disease using serum bilirubin and liver function tests. "Analysis of the data also reveals that the ratio of total cholesterol to serum total bilirubin may also be used as a predictor for CAD, particularly in place of using HDL-cholesterol or the ratio of total cholesterol to HDL-cholesterol. The advantage of using serum total bilirubin in place of HDL-cholesterol is that it is difficult to standardize tests for HDL-cholesterol" (column 10, lines 60-66).

9. U. S. Patent No. 5,396,886 (Cuypers) concerns a method for predicting coronary artery disease using a risk assessment diagram (see Figs. 1 and 2).

10. U. S. Patent No. 5,453,359 (Gargan et al.) concerns an in vitro immunoassay to detect and quantitate soluble cross-linked and non-crosslinked DesAABB fibrin polymers. The assay can be used to support a diagnosis of, to evaluate, and to monitor, in a mammalian subject, a thrombotic event, including, but not limited to, myocardial infarction, pulmoanry embolism, stroke, and deep vein thrombosis.

11. U. S. Patent No. 5,487,892 (Gargan) concerns a method for treating thrombotic disease using a fibrin-specific monoclonal antibody.

12. U. S. Patent No. 5,597,726 (Bumol et al.) concerns a naturally occurring, minimally modified LDL antigen which is present in atherosclerotic lesions as well as in the serum of a high percentage of patients with coronary artery disease. It also concerns antibodies,

including monoclonal antibodies, to that antigen and methods for using the antibodies in the diagnosis and treatment of atherosclerotic disease.

13. U. S. Patent No. 5,604,105 (Jackowski) concerns using at least three markers (and preferably four) to detect ischemic events of interest (column 10, lines 31-52). Each marker is "a protein or other molecule that is released from the heart during an ischemic event" (Abstract; column 13, lines 62-67; and column 14, line 25 et seq.).

14. U. S. Patent No. 5,658,729 (Hayden et al.) concerns a single point mutation in the human lipoprotein lipase gene that results in an A to G nucleotide change at codon 291 of the gene, which is associated with an increased susceptibility to coronary artery disease, including premature atherosclerosis. It also concerns a method, reagent, and kit for evaluating such susceptibility.

15. U. S. Patent No. 5,690,103 (Groth et al.) concerns detection/exclusion of acute myocardial infarction using neural networks analysis of measurements of at least two different biochemical markers that have different rates of appearance in plasma. Markers for myocardial damage include myoglobin, creatine kinase MB ("CK-MB"), troponin T, CK, CK-MM, CK-MB, LDH, LDH-5 (see column 1, line 56 et seq.).

16. U. S. Patent No. 5,710,008 (Jackowski) concerns using at least three markers (and preferably four) to detect ischemic events of interest (Abstract). Each marker is a protein that is released from the heart during an ischemic event (Abstract; column 8, lines 55-56; column 14, line 30 et seq.).

17. U. S. Patent No. 5,731,208 (Henicke) concerns a diagnostic method and screening test for atherosclerosis and analogous diseases involving activated phagocytes and/or inflammation. The method/test comprises determining the presence of p-hydroxyphenylacetaldehyde-lysine in a test sample of a body fluid or tissue at a level which is elevated relative to the level in a normal patient.

18. U. S. Patent No. 5,756,067 (Redgrave et al.) concerns a method for determining the presence of or propensity for atherosclerosis or coronary artery disease in a patient by administering to the patient a labeled diagnostic composition that mimics essential features of an exogenous lipoprotein transport particle (e.g., one which mimics the chemical formulation of a chyloremnant, preferably one that is lipidic) and measuring the quantity of

labeled metabolite in the bodily waste or blood of the patient to determine the quantity of labeled composition that has been metabolized.

19. U. S. Patent No. 6,040,147 (Ridker et al.) concerns methods for characterizing an individual's risk profile of developing a future cardiovascular disorder by obtaining a level of the marker of systemic inflammation in the individual (e.g., C-reactive protein) and also concerns methods for evaluating the likelihood that an individual will benefit from treatment with an agent for reducing the risk of future cardiovascular disorder. Fig. 2 is said to be a graph demonstrating the relative risks of future myocardial infarction associated with high, middle, and low tertiles of total cholesterol and C-reactive protein, and Fig. 3 is said to be a graph demonstrating the relative risks of future myocardial infarction associated with high, middle, and low tertiles of total cholesterol:HDL cholesterol ratio and C-reactive protein (column 5, lines 22-28). "It has been discovered that elevated levels of markers of systemic inflammation are predictive of future cardiovascular disorders. For example, elevated levels of markers of systemic inflammation in apparently healthy, nonsmokers are predictive of an increased risk of myocardial infarction. ... " (column 2, lines 24-35).

20. U. S. Patent No. 6,309,888 (Holvoet et al.) concerns a method having a clinically sufficient degree of diagnostic accuracy for detecting the presence of coronary artery disease in a human patient from the general population and for distinguishing between the stages of the disease in that patient. The stages are, first, the non-acute stage, which is either asymptomatic coronary artery disease or stable angina, second, the acute stage known as unstable angina, and, third, the acute stage known as acute myocardial infarction. The diseased state (as opposed to the non-diseased state) is indicated by the clinically significant presence of a first marker in a sample from the patient. The presence of one of the two acute stages, unstable angina or acute myocardial infarction, is indicated by the clinically significant presence of a second marker in a sample from the patient. The presence of the more severe acute stage known as acute myocardial infarction is indicated by the clinically significant presence of a third marker in a sample from the patient. Preferably the first marker comprises OxLDL, the second marker comprises MDA-modified LDL, and the third marker is a troponin. Preferably the OxLDL and MDA-modified LDL are detected using monoclonal antibodies that can detect the presence of those markers in undiluted human plasma at concentrations as low as 0.02 milligrams/deciliter. Substances discussed in the examples include OxLDL, MDA-modified LDL, HDL, and

C-reactive protein (see, e.g., Table III in column 18, Tables VI to IX in columns 21 to 22). The antibodies that can be used have high affinity and bind MDA-modified LDL and/or OxLDL whose apo B-100 moieties contain at least 60 substituted lysine residues per ap B-100 moiety (column 12, line 39, to column 13, line 8). The preferred monoclonal antibodies are mAb-4E6, mAb-1H11, and mAb-8A2 (column 13, line 9 et seq.).

21. U. S. Patent Application Publication No. 2003/0100486 (Ridker et al.) concerns methods for characterizing an individual's risk profile of developing future diabetes or complications of diabetes by obtaining a level of an inflammatory marker in the individual (preferably C-reactive protein or interleukin-6, which are markers of systemic inflammation) and also concerns methods for evaluating the likelihood that an individual will benefit from treatment with an agent for reducing the risk of future diabetes. See, e.g., paragraphs 0057, 0060, and 0064.

22. U. S. Patent Application Publication No. 2003/0152566 (Schonbeck et al.) concerns a diagnostic test for determining the risk of atherosclerotic diseases such as myocardial infarction and stroke, particularly among individuals with no signs or symptoms of current disease and among nonsmokers and also concerns a diagnostic test for assisting physicians in determining which individuals at risk will preferentially benefit from certain treatments designed either to prevent first or recurrent myocardial infarctions and strokes or to treat acute and chronic cardiovascular disorders. "Elevated levels of markers of inflammation have been shown previously to be predictive of future adverse cardiovascular disorders. This has not previously been demonstrated for sCD40L, a mediator of certain aspects of inflammation although not conventionally regarded previously as a systemic marker of inflammation." (paragraph 0009) "It has been discovered that elevated levels of sCD40L are predictive of future cardiovascular disorders. For example, elevated levels of sCD40L in apparently healthy, nonsmokers are predictive of an increased risk of myocardial infarction. As another example, elevated levels of sCD40L are predictive of an increased likelihood of a future stroke." (paragraph 0011) Example 2 (paragraphs 0131 to 0163) concluded that "Oxidatively modified LDL (oxLDL) concentration-dependently enhanced the faint constitutive expression of CD40 and CD40L protein in human vascular EC [endothelial cells] and MØ [mononuclear phagocytes]. ... Native LDL also induced expression of the receptor ... although to a lesser extent. Furthermore,

oxLDL concentration-dependently augmented the expression of CD40 and CD40L mRNA in human vascular EC or MØ." (paragraph 158)

23. EPO Published Application 0 327 418 A1 (in French; no translation) concerns an immunometric assay for lipoprotein particles containing apolipoprotein B and at least one other apolipoprotein (for example, apolipoprotein (a)), monoclonal antibodies, and a method for diagnosing atherosclerosis.

24. EPO Published Patent 0 433 088 B1 is related to U. S. Patent Nos. 5,196,324 and 5,597,726 (both discussed herein).

25. EPO Published Application 0 484 863 A1 concerns monoclonal antibodies to what the application refers to as human MDA-modified LDL and reduced type MDA-modified LDL.

26. PCT Published Application WO 94/23302 concerns immunodetection (e.g., ELISA) of oxidatively-modified low density lipoprotein, antibodies thereto (preferably monoclonal antibodies) or an immune complex thereof, in biological fluid, which is said to be useful in assessing the risk of coronary artery disease. Thus, e.g., monoclonal antibodies are said to be useful for detecting oxidatively-modified low density lipoprotein in human plasma (e.g., page 8, line 11 et seq.).

27. PCT Published Application WO 98/59248 concerns immunoassays for malondialdehyde-modified low density lipoprotein (MDA-modified LDL) and oxidized low density lipoprotein (OxLDL), monoclonal antibodies (and the cell lines for them) for use in the assays, and a storage-stable standard (which may be used as a calibrator and/or control). MDA-modified LDL and OxLDL are implicated in atherosclerosis and its etiology. The antibodies that can be used have high affinity and bind MDA-modified LDL and/or OxLDL whose apo B-100 moieties contain at least 60 substituted lysine residues per ap B-100 moiety (page 5, line 14, to page 6, line 6). The preferred monoclonal antibodies are mAb-4E6, mAb-1H11, and mAb-8A2 (page 6, lines 7-18).

28. PCT Published Application WO 00/14548 corresponds to U. S. Patent No. 6,309,888 (discussed herein).

29. JP Laid Open Patent Application (Kokai) No. 8-304395 concerns "a method for the determination of human oxidized lipoproteins whereby oxidized lipoproteins such as oxidized LDL in circulating blood are detected with high sensitivity and quantitatively by a

comparatively simple method" (translation, page 1, Abstract). The method uses "antibodies that recognize antigens that are produced oxidation of phospholipids" (Id.). "When antibodies that recognize antigens that are produced by oxidation of phosphatidylcholine in the presence of peptides or antibodies that are obtained by sensitizing suitable animals by means of atherosclerotic lesions are used, particularly good results are obtained" (Id.). The document also concerns a "method for diagnosing various types of circulatory system diseases using the aforementioned method [for the determination of human oxidized lipoproteins] including coronary artery disease such as myocardial infarction and angina pectoris, cerebrovascular diseases such as cerebral infarction and cerebrovascular dementia, renal artery diseases such as nephrosis and diabetic nephrosis and peripheral artery disease due to peripheral artery occlusion" (translation, Field of industrial use, pages 2-3; see also page 11). "If oxidized LDL is deeply related to progress of atherosclerotic lesions, it is clear that detection of oxidized lipoproteins such as oxidized LDL in circulating blood in high sensitivity and quantitatively must be established in early diagnosis of advances of pathological states" (translation, page 4). "This invention is also a method for the determination of human oxidized lipoproteins characterized in that plasma and/or lipoprotein separated from it is diluted to a suitable concentration, after which it is brought into contact with antibodies ... [with two antibodies, one of which can be made into a solid phase]" (Id.). "Because the antibodies of this invention ... that recognize the antigens that are produced by oxidation of phospholipids as described above are not dependent on the apoproteins of the recognizing epitopes, oxides of different lipoproteins in the blood can be evaluated individually" (Id. at page 6). The preferred antibody (FOH1a/DLH3) reacts with oxidized LDL but does not react with unmodified LDL or with malondialdehyde-modified LDL (page 9).

30. JP Laid Open Patent Application (Kokai) No. 9-5323 concerns "a simple and rapid method of determining the quantity of low specific gravity lipoprotein that is useful as an indicator for early discovery of coronary artery diseases such as atheroma arteriosclerosis or groups of diseases preliminary to such conditions and that have been chemically modified by oxidation in plasma or serum that has been subjected to oxidation treatment" (translation, page 1). "The method to determine oxidized LDL is characterized in that plasma or serum is treated by oxidation and in that the low specific gravity lipoprotein present in the plasma (or serum) that has been oxidatively modified (hereinafter abbreviated as LDL) is determined by an

immunological determination method using antibodies that have specificity for oxidized LDL" (Id.). "[I]t is thought that the capacity for LDL to undergo oxidation reflects the quantity of oxidized LDL that can be produced in the blood flow" (Id. at page 3). According to the document, there is "essentially no difference between the quantities of oxidized LDL actually present in the plasma (or serum) of normal persons and patients with coronary artery disease, in other words, that early discovery of coronary artery disease and groups [of diseases] which are precursors to such diseases was difficult using such findings [concerning the quantity of oxidized LDL in plasma or serum] as an indicator" (pages 3-4). However, when the LDL of normal individuals and patents with coronary artery disease was subjected to the oxidation treatment of the document, there was a "significant difference between them, in other words, that the quantities of oxidized LDL found in this way were useful as indicators for the early discovery of patients with coronary artery disease and groups [of diseases] which are precursors to these diseases" (page 4). The antibodies used have specificity for oxidized LDL and do not react with normal LDL (Id.). Preferred are monoclonal antibodies that "combine specifically with oxidized LDL, acetylated LDL and malondialdehyde modified LDL" (page 5). The monoclonal antibodies were obtained using an equimolar mixed solution of the acetylated LDL, malondialdehyde-modified LDL, and oxidized LDL prepared in Example 1 of the document (page 6). "As can be seen from Figure 3 and Table 3, there was essentially no difference between the quantity of natural oxidized LDL in CCU [cardiac care unit] serum and that in the serum of normal persons; in other words, the quantity of natural oxidized LDL cannot be used as an indicator for the purpose of early discovery of coronary artery disease such as atheromatous arteriosclerosis and groups [of diseases] which are precursors to these diseases" (page 11). The document indicates, however, that the quantity of easily oxidizable LDL is useful as such an indicator (Id.).

31. Adams JE, 3d, Bodor GS, Davila-Roman VG, Delmez JA, Apple FS, Ladenson JH, Jaffe AS, "Cardiac Troponin I. A Marker With High Specificity For Cardiac Injury," *Circulation* 1993; 88(1): 101-106, indicates that cardiac Troponin I is highly specific for myocardial injury and that its use should facilitate distinguishing whether elevations of MBCK are due to myocardial or skeletal muscle injury.

32. American Biogenetic Sciences Inc., *1995 Annual Report,* 24 pages (1995), concerns early detection of blood clot formation using "thrombus precursor protein" ("TpP").

The TpP assay is said to have high sensitivity and predictive value for ruling out heart attack in patients with chest pain (e.g., page 5). "The high predictive power of this test suggests its use as an early screen in an emergency room setting to differentiate between patients at risk of progression to MIs and non-MIs patients that present with similar clinical symptoms" (Id.) "Fibrinogen levels in the blood have been recently recognized as a potentially important independent risk factor for cardiovascular disease" (page 7). Monoclonal antibodies are used to detect the various analytes.

33. *American Biogenetic Sciences, Focus on Diagnostic Tests: A Technology Analysis. Updated Full Report,* 33 pages, Paisley and Habermas, Inc. (June 3, 1996), also concerns TpP (see preceding item) and points out that the TpP assay does not detect cell death but rather measures active or incipient thrombosis (page 2). A diagram on page 4 depicts coagulation and thrombus formation. "Elevated blood fibrinogen levels are recognized as a major risk factor for coronary heart disease" (page 18).

34. American Biogenetic Sciences, Inc., "Renal dialysis joint venture announced by American Biogenetic Sciences, Inc. and Gull Laboratories, Inc.," News Release (9/26/96), concerns the use of the TpP assay in connection with dialysis patients (see other American Biogenetic Sciences documents).

35. American Biogenetic Sciences, Inc., Jesup & Lamont Securities Corporation, "New Buy Recommendation dated March 28, 1996" (12 pages), concerns the TpP assay (see preceding items). "Recent research strongly suggests that fibrinogen is more predictive of cardiovascular disease than cholesterol" (page 8).

36. Antman EM, Tanasijevic MJ, Thompson B, Schactman M, McCabe CH, Cannon CP, Fischer GA, Fung AY, Thompson C, Wybenga D, Braunwald E, "Cardiac-Specific Troponin I Levels To Predict The Risk Of Mortality In Patients With Acute Coronary Syndromes," *N. Eng. J. Med.* 1996; 335(18): 1342-1349, concludes that "[i]n patients with acute coronary syndromes, cardiac troponin I levels provide useful prognostic information and permit the early identification of patients with an increased risk of death" (page 1342).

37. AtheroGenics, Inc. Printout of Web Site (WWW.ATHEROGENICS.COM), Home page and "Technology Platform" and "In The News" sections, 17 pages (printed June 8, 1998), indicates that "[a]therosclerosis is a multifactorial, inflammatory disease that is caused by so-called risk factors such as hypercholesterolemia ..." (second page). "There are currently no

diagnostic tools that exploit these advances in the biological basis of coronary disease that enable the physician to either diagnose the presence of atherosclerosis disease activity or the efficacy of therapy designed to cure the disease" (fifth page). "Oxykines™ are novel, oxidatively-modified factors generated in atherosclerosis that mediate inflammatory responses in vascular endothelial cells," and monoclonal antibodies are said to be in development (Id.).

38. Aviram M, Maor I, "Phospholipase D-Modified Low Density Lipoprotein Is Taken Up By Macrophages At Increased Rate, A Possible Role For Phosphatidic Acid," *J. Clin. Invest.* 1993; 91: 1942-1952, indicates that PLase D modification of LDL may take place under certain pathological conditions and PLase D-LDL interaction with arterial wall macrophages can potentially lead to foam cell formation (page 1942).

39. Berliner JA, Heinecke JW, "The Role Of Oxidized Lipoproteins In Atherogenesis," *Free Radical Biology & Medicine* 1996; 20(5): 707-727, is a review article. It indicates that there is considerable evidence that oxidized LDL and oxidized lipids can trigger the pathologic events of atherosclerosis and that oxidation may be important in the pathogenesis of human atherosclerosis (page 720). "Despite the intense interest in LDL oxidation, the central question of whether oxidized LDL is a causal agent in atherogenesis is still unanswered" (Id.). "Lipoprotein-like particles with oxidative damage have been isolated from atherosclerotic lesions .... Lipid oxidation products such as malondialdehyde have been immunohistochemically detected in human and animal atherosclerotic lesions ..." (page 707).

40. Boyd H, Gown AM, Wolfbauer G, Chait A, "Direct Evidence For A Protein Recognized By A Monoclonal Antibody Against Oxidatively Modified LDL In Atherosclerotic Lesions From A Watanabe Hyperlipidemic Rabbit," *Am. J. Pathol.* 1989 November; 135(5): 815-825, concerns oxidatively modified LDL. "Low density lipoproteins (LDL) that have been oxidatively modified have been implicated in the pathogenesis of atherosclerosis" (page 815). Monoclonal antibodies were generated against oxidatively modified human low density lipoprotein (OxLDL), which antibodies reacted with OxLDL but not with native LDL. The antibodies also reacted with other modified forms of LDL, e.g., acetylated LDL, MDA-modified LDL, and cell-modified LDL (Id.). The authors' "observations suggest that OxLDL (or possibly other proteins recognized by the anti-OxLDL antibody) is present in atheromatous lesions of WHHL rabbits, and are consistent with oxidatively modified lipoproteins having a role in atherogenesis" (Id.).

41. Brody, JE, "Hunt For Heart Disease Tracks A New Suspect," *The New York Times,* 3 pages (Jan. 6, 2004), notes that cardiovascular disease is "by far the leading cause of death for Americans" and that "[c]holesterol screening fails to identify 50 percent of the people who have heart attacks in the United States each year, because their total cholesterol is either normal or only moderately elevated" (page 1). "'It is apparent that a substantial proportion of cardiovascular events occurs in individuals without established risk factors' ... and so researchers are still looking for new factors that seem to increase risk of developing heart disease or dying from it." (Id.) "One emerging factor is a substance called C-reactive protein, or CRP. It is a natural chemical produced in the liver and released into the bloodstream in the presence of acute or chronic inflammation. High levels of the chemical may explain why some people with low cholesterol develop heart disease or why rigid adherence to a cholesterol-lowering diet sometimes fails to prevent serious heart problems." (Id.) "[S]ome experts believe that levels of C-reactive protein are better than cholesterol level at predicting future cardiac events" (page 2). "In March 2002, experts from the Centers for Disease Control and Prevention and the American Heart Association concluded that patients deemed to be at "intermediate risk" of a heart attack, stroke or other cardiovascular event should be tested for C-reactive protein." (page 3) "The experts, however, do not recommend CRP testing either for those at otherwise low risk of heart disease or for those known to be at high risk — those who already have signs of trouble, since they should already be getting aggressive treatment" (Id.).

42. Brown MS, Goldstein JL, "Lipoprotein Metabolism In The Macrophage: Implications For Cholesterol Deposition In Atherosclerosis," *Annu. Review Biochem.* 1983; 52: 223-261, reviews studies carried out during the then preceding five years concerning cholesterol uptake, storage, and excretion by macrophages. Malondialdehyde can react with the lysines of LDL and convert the lipoprotein to a form that is recognized with high affinity by macrophages (page 233).

43. Cartier R, Dagenais F, Hollmann C, Cambron H, Buluran J, "Chronic Exposure To Cyclosporin Affects Endothelial And Smooth Muscle Reactivity In The Rat Aorta," *Ann. Thorac. Surg.* 1994; 58: 789-794, indicates a potential explanation for the increased incidence of, among other things, thrombotic disease in transplanted patients treated with CyA as well as for premature coronary arteriosclerosis observed in heart transplant recipients (page 793).

44. Chapelle JP. "How Should We proceed When A Myocardial Infarction Is Suspected," *Acta Clinica Belgica* 1984; 39(6): 393-395, concerns diagnostic tests for acute myocardial infarction. "Consequently, to maximize the effectiveness of laboratory tests used in the diagnosis of MI [myocardial infarction] and to minimize costs, we recommend to use combinations of two tests; the strategy (selected tests and frequency of determinations) used to obtain maximum information depends however on the time elapsed between the onset of symptoms and the first blood sampling" (page 394, left column).

45. Chen CH, Nguyen HH, Weilbaecher D, Luo S, Gotto Jr. AM, Henry PD, "Basic Fibroblast Growth Factor Reverses Atherosclerotic Impairment Of Human Coronary Angiogenesis-Like Responses In Vitro," *Atherosclerosis* 1995; 116: 261-268, reports that inhibition of cell replication by oxidized low density lipoprotein was reversed by basic fibroblast growth factor, that human atherosclerosis is associated with impairment of angiogenesis-like endothelial growth, and that decreased basic fibroblast growth factor availability contributes to the impairment.

46. Chin JH, Azhar S, Hoffman BB, "Inactivation Of Endothelial Derived Relaxing Factor By Oxidized Lipoproteins," *J. Clin. Invest.* 1992; 89: 10-18, notes that LDL modified by oxidation has cytotoxic and atherogenic properties and that oxidized LDL in the artery wall, especially in atherosclerotic plaques, may be the atherogenic form of LDL (page 10).

47. Cockcroft DW, Gault MH, "Prediction of creatinine clearance from serum creatinine," *Nephron* 1976; 16: 31-41, provides a formula to predict such clearance.

48. Crisp SJ, Dunn JM, Rose ML, Barbir M, Yacoub MH, "Antiendothelial Antibodies After Heart Transplantation: The Accelerating Factor In Transplant-Associated Coronary Artery Disease?" *J. Heart Lung Transplant.* 1994; 13(1, Part 1): 81-92, notes that accelerated or transplant-associated coronary artery disease is the major long-term complication of heart transplantation and indicates that because accelerated coronary artery disease spares the recipient's own arteries, the most likely initiating event would appear to be an immune-mediated rejection response against antigens expressed on the donor coronary vasculature (page 81). The article suggests that monitoring such a patient's antibody levels may be of considerable prognostic and therapeutic value (page 90).

49. Declerck PJ, Mombaerts P, Holvoet P, De Mol M, Collen D, "Fibrinolytic Response And Fibrin Fragment D-Dimer Levels In Patients With Deep Vein Thrombosis,"

*Thromb. Haemost.* 1987; 58(4): 1024-1029, indicates that combined assays of total and free t-PA antigen and of fragments of D-dimer may be useful for the evaluation of the dynamics of the fribrinolytic system in physiological and pathological conditions (page 1024). "Fragment D-dimer may seems to be a marker of in vivo ongoing thrombosis, whereas lack of free t-PA response to venous occlusion may be indicative of a prethrombotic tendency (page 1028).

50. Degoulet P, Legrain M, Reach I, Aime F, Devries C, Rojas P, Jacobs C, "Mortality Risk Factors In Patients Treated By Chronic Hemodialysis," *Nephron* 1982; 31: 103-110, indicates that in addition to elevated blood pressure, a poor nutritional state and/or low protein intake may be important factors for explaining the high cardiovascular mortality, particularly for strokes, observed in dialysis patients. At page 108, the article indicates the difficulty of applying results obtained in a general population to a population of dialyzed patients.

51. Esterbauer H, Jurgens G, Quehenberger Q, Koller E, "Autooxidation Of Human Low Density Lipoprotein: Loss Of Polyunsaturated Fatty Acids And Vitamin E And Generation Of Aldehydes," *J. Lipid Res.* 1987; 28: 495-509, indicates at page 495 that modification of LDL by oxidative processes results in an enhanced uptake by the scavenger receptor macrophages and that this altered functionality might, in vivo, affect cholesterol metabolism and lead to a conversion of macrophages into the lipid-laden foam cells that are constituents characteristic of the atherosclerotic plaques. At page 507, it indicates that modification of LDL with malondialdehyde leads to an enhanced uptake of LDL by human monocyte macrophages followed by cholesteryl ester accumulation, and reference is made to work that is said to demonstrate that the uptake of MDA-modified LDL by the scavenger receptor of monocyte macrophages occurred only above a threshold neutralization of 60 mol of lysine residues/mol of LDL by malondialdehyde.

52. Farber HW, Barnett HF, "Differences In Prostaglandin Metabolism In Cultured Aortic And Pulmonary Arterial Endothelial Cells Exposed To Acute And Chronic Hypoxia," *Circ. Res.* 1991; 68(5): 1446-1457, concerns the hypothesis that the anatomic location of the endothelial cells and the duration and degree of hypoxia are important factors in endothelial cell cytokine release following exposure to hypoxia.

53. Fogelman MA, Shechter I, Seager J, Hokom M, Child JS, Edwards PA, "Malondialdehyde Alteration Of Low Density Lipoproteins Leads To Cholesteryl Ester

Accumulation In Human Monocyte-Macrophages," *Proc. Natl. Acad. Sci. USA* 1980; 77(4): 2214-2218, speculates that modification of native LDL may be a prerequisite to the accumulation of cholesteryl esters within the cells of the atherosclerotic reaction and that one modification of LDL in vivo may result from malondialdehyde which is released from blood platelets or is produced by lipid peroxidation at the site of arterial injury.

54. Folcik VA, Nivar-Aristy RA, Krajewski LP, Cathcart MK, "Lipoxygenase Contributes To The Oxidation Of Lipids In Human Atherosclerotic Plaques," *J. Clin. Invest.* 1995; 96: 504-510, indicates that strong evidence has accumulated supporting the concept that oxidative processes, acting on the lipids and proteins of LDL in the vessel wall, participate in the progression of atherosclerotic disease. It also notes that oxidized LDL is present in human atherosclerotic lesions, but that the mechanisms responsible for oxidation in vivo have not been definitely demonstrated.

55. Friedman JA, Dwyer JT, "Hyperhomocysteinemia As A Risk Factor For Cardiovascular Disease In Patients Undergoing Hemodialysis," *Nutr. Rev.* 1995; 53(7): 197-201, notes that hyperhomocysteinemia exists among patients both in end-stage renal disease and on dialysis and may represent an additional risk factor for increased cardiovascular disease. It also notes that supplementation with folic acid may reduce, but not correct, hyperhomocysteinemia and that evidence that lowering blood homocysteine will lessen cardiovascular disease is still being sought. It also notes that such patients have age-adjusted cardiovascular-related morbidity and mortality rates twice that of their healthy peers.

56. Galle J, Bengen J, Schollmeyer P, Wanner C, "Oxidized Lipoprotein(A) Inhibits Endothelium-Dependent Dilation: Prevention By High Density Lipoprotein," *Eur. J. Pharmacol.* 1994; 265: 111-115, reports that oxidized lipoprotein(a) impairs endothelium-dependent vasodilation and that HDL prevents its inhibitory effect.

57. Galle J, Schollmeyer P, Wanner C, "Cyclosporin And Oxidized Low Density Lipoproteins Synergistically Potentiate Vasoconstriction: Influence Of The Endothelium," *Eur. Heart J.* 1993; 14(Suppl. I): 111-117, reports that co-incubation of isolated renal arteries with CyA and Ox-LDL potentiates norepinephrine-induced vasoconstriction by a $Ca^{+2}$ and partially endothelium-dependent mechanism, which may contribute to CyA-induced hypertension and nephrotoxicity.

58. Gerrity RG, "The Role Of The Monocyte In Atherogenesis. I. Transition Of Blood-Borne Monocytes Into Foam Cells In Fatty Lesions," *Am. J. Pathol.* 1981; 103(2): 181-190, reports that blood mononuclear cells associated with lesion formation in the model used are monocytes, which subsequently undergo transformation into macrophage foam cells in fatty streak lesions and that the absence of medial cell involvement indicates that monocytes are the major foam cell precursor in these lesions.

59. Grattan MT, Moreno-Cabral CE, Starnes VA, Oyer PE, Stinson EB, Shumway NE, "Cytomegalovirus Infection Is Associated With Cardiac Allograft Rejection And Atherosclerosis," *J. Am. Med. Assoc.* 1989; 261(24): 3561-3566, reports that cytomegalovirus infection in cardiac transplant recipients is associated with more frequent rejection, graft atherosclerosis, and death.

60. Haberland MD, Fogelman AM, Edwards PA, "Specificity Of Receptor-Mediated Recognition Of Malondialdehyde-Modified Low Density Lipoproteins," *Proc. Natl. Acad. Sci USA.* 1982; 79: 1712-1716, reports that a minimum of 30 mol of malondialdehyde/mol of LDL (60 lysine residues) is required to stimulate recognition by the scavenger receptor of human monocyte macrophages, if the modification is conducted with LDL maintained in solution (page 1716). "[I]t is anticipated that, in disease states in which modification of LDL may occur, such as atherosclerosis or diabetes, a small but significant proportion of circulating LDL may contain partially modified lipoprotein" (Id.).

61. Haberland ME, Olch CL, Fogelman AM, "Role Of Lysines In Mediating Interaction Of Modified Low Density Lipoproteins With The Scavenger Receptor Of Human Monocyte Macrophages," *J. Biol. Chem.* 1984; 259(18): 11305-11311, indicates that there is substantial evidence that blood monocytes are precursors of certain foam cells in the early stages of atherogenesis (page 11305). It also notes that the authors have previously demonstrated that neutralization of up to 16% of the lysine residues of the apo-B polypeptide of LDL by malondialdehyde, or up to 60 mol lysine/mol of LDL, results in recognition and uptake of the modified lipoprotein by the LDL receptor in human monocyte macrophages, and that further modification of the LDL results in threshold recognition and endocytosis by the scavenger receptor with concomitant loss of recognition by the LDL receptor (Id.). This article reports on ability of the scavenge receptor of human monocyte macrophages to recognize human LDL that

has been progressively modified by three lysine-specific reagents, namely, malondialdehyde, acetic anhydride, and succinic acid.

62. Hamm WC, Goldmann BU, Heeschen C, Kreymann G, Berger J, Meinertz T, "Emergency Room Triage Of Patients With Acute Chest Pain By Means Of Rapid Testing For Cardiac Troponin T Or Troponin I," *N. Eng. J. Med.* 1997; 337(23): 1648-1653, reports on the evaluation of patients with chest pain for the presence of troponin T and troponin I using monoclonal antibodies. Among 47 patients with evolving myocardial infarction, troponin T tests were positive in 44 (94 percent) and troponin I tests were positive in all 47. Among 315 patients with unstable angina, troponin T tests were positive in 70 patients (22 percent) and troponin I tests were positive in 114 patients (36 percent). The authors concluded that bedside tests for cardiac-specific troponins are highly sensitive for the early detection of myocardial-cell injury in acute coronary syndromes and that negative tests are associated with low risk and allow rapid and safe discharge of patients with an episode of acute chest pain from the emergency room.

63. Hamm WC, Goldmann BU, Heeschen C, Kreymann G, Berger J, Meinertz T, "Emergency Room Triage Of Patients With Acute Chest Pain By Means Of Rapid Testing For Cardiac Troponin T Or Troponin I," *N. Eng. J. Med.* 1997; 337(23): 1648-1653: Letters concerning same and authors' reply, published in *N. Eng. J. Med.* 1998; 338(18): 1314-1315. In various letters to the editor, other doctors indicate their concern with some of the conclusions in the main article and with possible bias of the test against troponin T as compared to troponin I.

64. Hammer A, Kager G, Dohr G, Rabl H, Ghassempur I, Jurgens G, "Generation, Characterization, And Histochemical Application Of Monoclonal Antibodies Selectively Recognizing Oxidatively Modified ApoB-Containing Serum Lipoproteins," *Arterioscler. Thromb. Vasc. Biol.* 1995; 15(5): 704-713, reports the production of monoclonal antibodies against a number of species, including OxLDL and MDA-modified LDL. It says that monoclonal are an important tool for investigating either the role oxidized LDL plays in atherosclerosis or structural changes on the surface of oxidized LDL (page 704). It also says that those monoclonal antibodies will bring about further insights into the distribution of oxidized apoB-containing lipoproteins in atherosclerotic plaques and that they might be used to establish immunoassays for the investigation of a possible presence of modified or oxidized apoB-containing lipoproteins in circulating human blood (page 712).

65. Hansson GK, Libby P. (eds.), *Immune Functions of the Vessel Wall*, Volume II (Harwood Academic Publishers 1996), Chapter 9: Witztum JL, Palinski W, "Autoimmunity To Oxidized Lipoproteins," pages 159-171, states that the data so far indicate that autologous modifications of LDL are immunogenic, that oxidation of LDL does occur in vivo, and that subsequently there is a humoral immune response. It also states that preliminary epidemiological data indicate that there is an increased titers of antibodies to epitopes of oxidized LDL in subjects with varying manifestations of atherosclerotic disease or increased risk factors for disease (page 164). See also Table 1, reporting increased titers of antibodies for human subjects with various diseases (page 162). The authors used MDA-modified LDL for study because MDA-modified LDL can be generated quite reproducibly, whereas the oxidation of LDL with copper yields highly variable preparations and less extensively modified preparations may continuously oxidize over time (page 164). The also state that the MDA-lysine epitope is abundantly present in lesions and circulating autoantibodies to MDA-modified LDL are prevalent (Id.). LDL was isolated from WHHL rabbits and modified so that more than 75% of the lysine residues were derivatized (Id.). "Although it is highly unlikely that extensively oxidized LDL exists in plasma, because any such oxidized LDL would be rapidly removed by sinusoidal scavenger receptors, it is certainly possible that minimally oxidized forms of LDL exist. Indeed, evidence has been presented that small numbers of such minimally oxidized LDL particles are present in plasma" (citing two papers, including Holvoet et al., *J. Clin. Invest.* 1995; 95: 2611-2619, below) (page 166).

66. Havel RJ, Eder HA, Bragdon JH, "The Distribution And Chemical Composition Of Ultracentrifugally Separated Lipoproteins In Human Serum," *J. Clin. Invest.* 1955; 34: 1345-1353, concerns separation of human lipoproteins.

67. Heery JM, Kozak M, Stafforini DM, Jones DA, Zimmerman GA, McIntyre TM, Prescott SM, "Oxidatively Modified LDL Contains Phospholipids With Platelet-Activating Factor-Like Activity And Stimulates The Growth Of Smooth Muscle Cells," *J. Clin. Invest.* 1995; 96: 2322-2330, indicates that oxidative modification of lipoproteins is believed to be important in the genesis of atherosclerosis, that increased levels of LDL are strongly associated with an increased risk of atherosclerosis, that there is evidence that LDL must be modified to become pathogenic, and that modification may be accomplished in vitro by a variety of chemical methods, including oxidation (page 2322). Aldehydes and other reactive compounds are formed

from the polyunsaturated fatty acids during oxidation of LDL, and these compounds can derivatize the apoprotein (pages 2328-2329).

68. Hirschfield GM, Pepys MB, "C-reactive protein and cardiovascular disease: new insights from an old molecule," *Q J Med.* 2003 Nov; 96(11): 793-807, notes that "[t]he classical acute-phase protein, C-reactive protein (CRP), is an exquisitely sensitive systemic marker of disease with broad clinical utility for monitoring and differential diagnosis. Inflammation, the key regulator of CRP synthesis, plays a pivotal role in atherothrombotic cardiovascular disease. There is a powerful predictive association between raised serum CRP values and the outcome of acute coronary syndromes, and, remarkably, between even modestly increased CRP production and future atherothrombotic events in otherwise healthy individuals. Baseline CRP values also reflect metabolic states associated with atherothrombotic events. The presence of CRP within most atherosclerotic plaques and all acute myocardial infarction lesions, coupled with binding of CRP to lipoproteins and its capacity for pro-inflammatory complement activation, suggests that CRP may contribute to the pathogenesis and complications of cardiovascular disease." Native, non-aggregated, human CRP does not bind to native LDL but does bind to oxidized LDL (pages 797 and 800). "The commercial availability of routine high-sensitivity assays for CRP has enabled a flood of studies demonstrating a powerful predictive relationship between increased CRP production, even within the range previously considered to be normal, and atherothrombotic events .... Circulating CRP values correlate closely with other markers of inflammation, some of which show similar, albeit generally less significant, predictive associations. However CRP itself is particularly interesting with respect to cardiovascular biology and pathology, because not only does it bind selectively to LDL, especially oxidized and enzyme-modified LDL as found in atheromatous plaques, but it is actually deposited in the majority of such plaques and it has a range of pro-inflammatory properties that could potentially contribute to the pathogenesis, progression and complications of atheroma." (page 798; citations omitted) "The predictive power for future cardiovascular disease ... may even be stronger for CRP than for LDL cholesterol, and there is evidence that increased CRP values identify individuals at risk who are not detected, for example, by the Framingham risk score. However, it is critically important to recognize that the CRP response is non-specific and is triggered by many disorders unrelated to cardiovascular disease. In using

CRP for cardiovasular risk assessment, it is therefore essential to clearly establish true baseline CRP values, not distorted by either trivial or serious intercurrent pathologies." (pages 799-800)

69. Hlatky MA, "Evaluation Of Chest Pain In The Emergency Department," *N. Eng. J. Med.* 1997; 337(23): 1687-1689, reports that after patients in the emergency department having clear-cut acute myocardial infarction have been identified, the remaining patients are more difficult to sort out; that symptoms suggestive of myocardial ischemia at rest that last more than 15 minutes indicate a relatively high short-term risk, probably because of their association with ruptured coronary plaque; that further tests used for patients include those that identify a defect in myocardial perfusion, abnormalities in left ventricular wall motion, or subtle evidence of myocardial necrosis though sensitive assays of intracellular proteins (e.g., CK-MB isoenzyme, myoglobin, troponin T, and troponin I); that even a highly sensitive marker of myocardial necrosis will not necessarily be positive in all patients with acute myocardial ischemia; and that patients who present for the first time with chest pain usually need further tests to establish the likelihood of underlying coronary disease and to guide appropriate therapy.

70. Hoff HF, O'Neill J, "Lesion-Derived Low Density Lipoprotein And Oxidized Low Density Lipoprotein Share A Lability For Aggregation, Leading To Enhanced Macrophage Degradation," *Arterioscler. Thromb.* 1991; 11(5): 1209-1222, states that the results reported suggest that oxidation may be a major mode of modification of LDL accumulating in atherosclerotic lesions. Specific chemical modification of LDL, such as acetylation or interaction with malondialdehyde, leads to LDL uptake by macrophages by a high-affinity binding site that has been designated the scavenger receptor (page 1209). Minced aortic atherosclerotic plaques obtained at autopsy ("A-LDL") and OxLDL share numerous structural and functional characteristics, suggesting that one of the modifications found in A-LDL is oxidation (page 1210). Using a monoclonal antibody that recognizes MDA-protein adducts, the authors found the both A-LDL and OxLDL interacted with it in a concentration-dependent fashion (page 1213 and, e.g., Figure 6 on page 1216).

71. Hoff HF, O'Neill J, Chisolm III GM, Cole TB, Quehenberger O, Esterbauer H, Jurgens G, "Modification Of Low Density Lipoprotein With 4-Hydroxynonenal Induces Uptake By Macrophages," *Arteriosclerosis* 1989; 9(4): 538-549, states that there is growing evidence that LDL may be subjected to oxidative modification in vivo and that oxidized LDL may occur both in the plasma compartment and in the interstitial space of the arterial intima.

Monoclonal antibodies directed at B-100 in LDL and MDA-modified proteins co-localize to sites in lesions from WHHL rabbits, suggesting that the LDL in the atherosclerotic lesion has been modified by MDA (pages 538-539).

72. Hoffmeister HM, Jur M, Wendel HP, Heller W, Seipel L, "Alterations Of Coagulation And Fibrinolytic And Kallikrein-Kinin Systems In The Acute And Post-Acute Phases In Patients With Unstable Angina Pectoris," *Circulation* 1995; 91(10): 2520-2527, reports that in patients with unstable angina, intracoronary thrombus fomration is associated with a hypercoagulative state, including activation of the contact phase and of the lallikrein system and increased bradykinin generation, and that the persistence of this hypercoagulative state, together with a distributed fibrinolysis, might indicate an increased risk for further coronary events. "Patients with coronary heart disease and stable exertional angina pectoris had higher fibrinogen levels ... compared with the control subjects ..." (page 2524). "Elevated levels of fibrinogen and of plasminogen, as observed in the patients with unstable angina pectoris, have been reported to a lesser extent, even in patients with stable angina pectoris. Marked elevation in fibrinogen was found in patients with acute myocardial infarction. Its elevation was attributed to both increased levels in patients with stable angina pectoris and coronary heart disease and the 'acute phase' reaction. In patients with unstable angina pectoris, the latter was also evident in the increase of the C-reactive protein, which was described as increasing similar to fibrinogen in patients with acute coronary syndromes. Other groups did not observe a significant increase in fibrinogen or a decrease of the factor XII levels in patients with unstable angina pectoris compared with the significant changes found in patients with acute myocardial infarction. Differing findings in the behavior of fibrinogen in several studies might result from the use of different populations, varying severity of the ischemic burden, and variations in the time of blood sampling." (page 2525)

73. Holvoet P, Perez G, Bernar H, Brouwers E, Vanloo B, Rosseneu M, Collen D, "Stimulation With A Monoclonal Antibody (mAb4E4) Of Scavenger Receptor-Mediated Uptake Of Chemically Modified Low Density Lipoproteins By THP-1-Derived Macrophages Enhances Foam Cell Generation," *J. Clin. Invest.* 1994; 93: 89-98, concerns monoclonal antibody mAb4E4, which is a murine monoclonal antibody that is specific for acetylated LDL and MDA-modified LDL but not for native LDL, and which binds specifically to modified LDL present in human atherosclerotic lesions. Binding constants for mAb-4E4 and for several other

monoclonal antibodies are described (e.g., page 91). At page 97, the article notes that the recent finding that serum levels of autoantibodies against oxidized LDL correlate with progression of carotid atherosclerosis might be indicative for immunoglobin enhanced foam cell generation, that activation of the immune system may be linked to the pathophysiology of evolving atheroma, and a hypothesis that formation of immune complexes within the plaques may contribute to the further progression of atherosclerotic lesions.

74. Holvoet P, Collen D, "Beta-VLDL Hypercholesterolemia Relative To LDL Hypercholesterolemia Is Associated With Higher Levels Of Oxidized Lipoproteins And A More Rapid Progression Of Coronary Atherosclerosis In Rabbits," *Arterioscler. Thromb. Vasc. Biol.* November 1997; 17(11): 2376-2382, uses monoclonal antibody mAb-4E6 to investigate the correlation between levels of oxidized beta-VLDL and LDL and the progression of lesions in coronary arteries of hypercholesterolemic rabbits that are primarily due to smooth muscle cell proliferation and foam cell formation and not to monocyte/macrophage accumulation. The antibody was used to detect oxidized apoB-100 containing lipoproteins. At page 2381 it is noted that recently "[w]e demonstrated oxidized LDL in the coronary artery lesions of ischemic heart disease patients, and we found a strong correlation between plasma levels of oxidized LDL and the extent and the progression of posttransplant coronary artery stenosis in heart transplant patients."

75. Holvoet P, Collen D, "Oxidized Lipoproteins In Atherosclerosis And Thrombosis," *FASEB J.* 1994; 8: 1279-1284, describes the biochemical nature of oxidative changes in LDL and the current evidence for the involvement of oxidized LDL in atherosclerosis and thrombosis. Evidence for the presence of oxidized LDL in atherosclerotic lesions and monoclonal antibodies mAb-4E4 and mAb-1H11 is discussed ed at page 1280. Evidence for the presence of oxidized LDL in plasma is discussed at page 1280.

76. Holvoet P, Collen D, "Thrombosis And Atherosclerosis," *Curr. Opinion Lipidol.* 1997; 8: 320-328, discusses the association between endothelial injury and increased leukocyte extravasation and platelet adhesion, via the promotion of selectin and von Willebrand factor expression and decreased anticoagulant activity of endothelium by affecting nitric oxide activity, interfering with thrombomodulin expression and inactivating tissue factor pathway inhibitor. "The initial step in atherosclerosis is the rapid targeting of monocytes to sites of inflammation or tissue injury" (page 320). "Elevated fibrinogen levels constitute a strong

independent risk factor for myocardial infarction .... The mechanisms by which fibrinogen contributes to atherogenesis remain hypothetical and may be related to fibrin formation, increases in blood viscosity, inflammation, platelet aggregation, expression of a preexisting thrombophilia and stimulation of smooth muscle cell proliferation." (page 323)

77. Holvoet P, Perez G, Zhao Z, Brouwers E, Bernar H, Collen D, "Malondialdehyde-Modified Low Density Lipoproteins In Patients With Atherosclerotic Disease," *J. Clin. Invest.* 1995; 95: 2611-2619, discusses mAb-1H11 monoclonal antibody, which was raised against MDA-modified LDL and which was used to detect cross-reacting material in human atheromatous tissue and in plasma. The apo B-100 molecules of in vitro MDA-modified LDL used for calibration of the assay were found to contain on average 244 modified lysines out of a total of 356, and the apo B-100 molecules of copper-oxidized LDL were found to contain an average of 210 modified lysines (page 2613). Inhibition curves for MDA-modified LDL, copper-oxidized LDL, and native LDL are shown on page 2613. Levels of MDA-modified LDL in plasma of control subjects, patients with chronic stable angina, patients with acute myocardial infarction, and patients with carotid atherosclerosis are reported. Elevated plasma levels of atherogenic MDA-modified LDL may be a marker for unstable atherosclerotic cardiovascular disease (pages 2611 and 2618).

78. Holvoet P, Donck J, Landeloos M, Brouwers E, Luijtens K, Arnout J, Lesaffre E, Vanrenterghem Y, Collen D, "Correlation Between Oxidized Low Density Lipoproteins And Von Willebrand Factor In Chronic Renal Failure," *Thromb. Haemost.* 1996; 76(5): 663-669, reports that an ELISA specific for a wide spectrum of oxidized apo B-100 in OxLDL was developed and applied to blood samples from control subject, mild chronic renal failure patients, and two groups of severe chronic renal failure patients. Statistical analysis revealed that the extent of renal failure accounted for a significant fraction of the variation in OxLDL levels. Atherogenic OxLDL increased progressively during the development of renal failure suggesting that the oxidation of LDL may be associated with endothelial injury and atherogenesis in these patients. The ELISA used monoclonal antibody mAb-4E6, which identified OxLDL having at least 60 substituted lysines per apo B-100 molecule (page 667). The lower limit of detection was 0.020 milligrams/deciliter in undiluted human plasma (page 665). Figure 1 shows the specificity of that antibody for OxLDL, MDA-modified LDL, and native

LDL. OxLDL may contribute to the progression of atherosclerosis and have been demonstrated in human atherosclerotic plaques (page 667).

79. Holvoet P, Van Kleemput J, Collen D, Vanhaecke J, "Correlation Between Oxidized Low Density Lipoproteins And Coronary Artery Disease In Heart Transplant Patients," Abstract published in *Final Programme* of 66th Congress of the European Atherosclerosis Society, Florence (Italy), July 13-14, 1996; *Abstract Book*, page 47, indicates that rapidly progressing coronary artery disease is a main complication of heart transplantation and that OxLDL may play a role in its pathogenesis. An ELISA using a monoclonal antibody was used to determine OxLDL in cardiac explants of patients with ischemic heart disease. Plasma OxLDL levels correlate with the extent of posttransplant coronary artery stenosis, and increased plasma levels of OxLDL may therefore be an early indicator of posttransplant coronary artery disease.

80. Holvoet P, Stassen JM, Van Cleemput J, Collen D, Vanhaecke J, "Oxidized Low Density Lipoproteins In Patients With Transplant-Associated Coronary Artery Disease," *Arterioscler. Thromb. Vasc. Biol.* January 1998; 18(1): 100-107, reports that an ELISA using monoclonal antibody mAb-4E6 was used to quantify levels of OxLDL in the plasma of control patients, patients transplanted (heart transplants) for dilated cardiomyopathy, and patients transplanted (heart transplants) for coronary artery disease. Plasma levels of OxLDL correlated with the extent of coronary artery disease in heart transplant patients and the study suggests that elevated levels of oxidized LDL may be a marker for patients at increased risk of posttransplant coronary artery disease (page 104). "The heart transplant population may provide us more rapidly with an answer as to the value of antioxidant therapy, inasmuch as posttransplant coronary artery stenosis could service as a paradigm for an accelerated form CAD in general" (page 105). "In a preliminary study, we found that levels of OxLDL were very similar in patients with ischemic heart disease, as evidenced by recurrent acute myocardial infarction, and in patients with posttransplant CAD, suggesting that oxidized LDL may indeed by a marker for CAD" (Id.). MDA-modified LDL also reacted with mAb-4E6 (page 101). Acute myocardial infarction is associated with an increase of plasma levels of MDA-modified LDL, suggesting that leakage from arterial lesions may be a source of oxidatively modified LDL in the plasma (page 106).

81. Holvoet P, Theilmeier G, Shivalkar B, Flameng W, Collen D, "LDL Hypercholesterolemia Is Associated With Accumulation Of Oxidized LDL, Atherosclerotic

Plaque Growth, And Compensatory Vessel Enlargement In Coronary Arteries Of Miniature Pigs," *Arterioscler. Thromb. Vasc. Biol.* 1998; 18: 415-422, concerns the association between accumulation of oxidized LDL and (1) progression of atherosclerotic plaques and (2) compensatory enlargement in the coronary arteries of LDL-hypercholesterolemic miniature pigs. Monoclonal antibodies are used, including mAb-4E6.

82. Holvoet P, Collen D, Vanhaecke J, Presentation at 70th Scientific Session Of The American Heart Association, Orlando, Florida, November 9-12, and published in abstract form in *Circulation* 1997; 96(Suppl. I): I417 (Abstract 2328), concerns an investigation of the hypothesis that oxidized LDL are associated with coronary artery disease. From the patients studied, it was concluded that coronary artery disease was associated with increased plasma levels of oxidized LDL.

83. Holvoet P, Vanhaecke J, Janssens S, Van de Werf F, Collen D, "Oxidized LDL And Malondialdehyde-Modified LDL In Patients With Acute Coronary Syndromes And Stable Coronary Artery Disease," *Circulation* 1998; 98: 1487-1494, indicates that the association between oxidative modifications of LDL and coronary artery disease (CAD) is suspected but not established and, therefore, that the association between plasma levels of oxidized LDL and malondialdehyde (MDA)-modified LDL and acute coronary syndromes and stable CAD was investigated. The authors wanted to compare plasma levels of oxidized and MDA-modified LDL in patients with acute coronary syndromes and patients with stable CAD and to study the association between oxidized LDL and MDA-modified LDL, respectively, and troponin I, a marker of ischemic syndromes, and C-reactive protein, a marker of inflammation. Plasma levels of MDA-modified LDL were significantly higher in patients with acute coronary syndromes than in individuals with stable CAD ($r^2$=0.65; $P$=0.0001) and were associated with increased levels of troponin I and C-reactive protein ($r^2$=0.39 and $r^2$=0.34, respectively; both $P$=0.0001). Plasma levels of oxidized LDL were not associated with increased levels of troponin I and C-reactive protein ($r^2$=0.089 and $r^2$=0.063, respectively). In agreement with previously published data, C-reactive protein was found to be a marker of acute coronary syndromes (Table 2). The conclusions were that elevated plasma levels of oxidized LDL are associated with CAD and that elevated plasma levels of MDA-modified LDL suggest plaque instability and may be useful for the identification of patients with acute coronary syndromes. Monoclonal antibody mAb-4E6 was used for the quantification of oxidized LDL in plasma and monoclonal antibody mAb-1H11

was used for the quantification of MDA-modified LDL in plasma (page 1488, left column, "Assays").

84. Holvoet P, Collen D, Van de Werf F, "Malondialdehyde-Modified LDL As A Marker Of Acute Coronary Syndromes," *J. Am. Med. Assoc.* 1999; 281(18): 1718-1721, reports the results of a study of 168 patients to determine the usefulness of MDA-modified LDL for identifying patients with unstable angina and acute myocardial infarction. MDA-modified LDL, but not troponin I or C-reactive protein, discriminated between stable CAD and unstable angina. Troponin I, but not MDA-modified LDL or C-reactive protein, discriminated between unstable angina and AMI. Both MDA-modified LDL and troponin I but not C-reactive protein discriminated between stable CAD and AMI. The conclusion was that the combination of MDA-modified LDL, which may reflect endothelial injury or plaque instability, and troponin I, which reflects myocardial cell injury, allows better discrimination between stable coronary artery disease and acute coronary syndromes than troponin I alone. "In the present study, the rather low diagnostic values of C-reactive protein and troponin I for unstable angina were confirmed ..." (page 1721).

85. Holvoet P, "Oxidative Modification Of Low-Density Lipoproteins In Atherothrombosis," *Acta Cardiol.* 1998, 53(5): 253-260, notes an association between coronary artery disease and increased plasma levels of oxidized LDL. "[P]lasma levels of oxidised LDL were very similar in patients with stable coronary artery disease and in patients with acute coronary syndromes. Acute coronary syndromes were, however, associated with increased release of malondialdehyde-modified LDL that was independent of necrosis of myocardial cells. Indeed, plasma levels of malondialdehyde-modified LDL were very similar in patients with unstable angina and patients with acute myocardial infarction, in contrast with levels of troponin I which were significantly higher in acute myocardial infarction patients. These data suggest that oxidised LDL is rather a marker of coronary atherosclerosis whereas malondialdehyde-modified LDL is rather a marker of plaque instability and atherothrombosis." (Abstract) "In vitro and in vivo data in experimental animal models suggest an association between atherothrombosis and oxidised LDL. ... In spite of a tremendous amount of in vitro data and in vivo data in experimental animal models, we still do not know whether oxidatively modified LDL has an active role in atherothrombosis in man." (page 258)

86. Holvoet P, Mertens A, Verhamme P, Bogaerts K, Beyens G, Verhaeghe R, Collen D, Muls E, Van de Werf F, "Circulating oxidized LDL is a useful marker for identifying patients with coronary artery disease," *Arterioscler Thromb Vasc Biol.* 2001 May; 21(5): 844-848, concerns determining the usefulness of circulating oxidized low density lipoprotein (LDL) in the identification of patients with coronary artery disease (CAD). A total of 304 subjects were studied. The Global Risk Assessment Score (GRAS) was calculated on the basis of age, total and high density lipoprotein cholesterol, blood pressure, diabetes mellitus, and smoking. Levels of circulating oxidized LDL were measured in a monoclonal antibody 4E6-based competition ELISA. Logistic regression analysis revealed that the predictive value of oxidized LDL was additive to that of GRAS ($P<0.001$). Ninety-four percent of the subjects with high (exceeding the 90th percentile of distribution in control subjects) circulating oxidized LDL and high GRAS had CAD (94% of the men and 100% of the women). Thus, circulating oxidized LDL is a sensitive marker of CAD. Addition of oxidized LDL to the established risk factors may improve cardiovascular risk prediction. (Abstract) "The relationship between circulating oxidized LDL and other potential risk factors, such as Lp(a) and homocysteine, has not yet been studied. However, to date, data demonstrating the additive value of Lp(a) and homocysteine to lipid measurement for cardiovascular risk prediction are inconsistent. Recently, measurement of high sensitivity C-reactive protein in addition to lipid measurement has been shown to cause significant improvement in clinical prediction models based on lipids alone in men and women [citing two articles by Ridker et al., both discussed herein]. However, high sensitivity measurements of C-reactive protein were not possible in the present study." (page 848)

87. Holvoet P, Harris TB, Tracy RP, Verhamme P, Newman AB, Rubin SM, Simonsick EM, Colbert LH, Kritchevsky SB, "Association of high coronary heart disease risk status with circulating oxidized LDL in the well-functioning elderly: findings from the Health, Aging, and Body Composition study," *Arterioscler Thromb Vasc Biol.* 2003 Aug; 23(8): 1444-1448, reports a study conducted to determine whether there is an association between high, predicted CHD (coronary heart disease) risk and OxLDL. The cohort included 385 persons with CHD and 1183 persons at high risk; the latter were all persons with CHD risk equivalents: noncoronary forms of clinical atherosclerotic disease, diabetes, and a 10-year risk for CHD >20% by Framingham scoring. The remaining 1535 participants were at low risk. Levels of OxLDL were 1.18+/-0.61 mg/dL for low-risk persons, 1.50+/-0.81 mg/dL for high-risk persons

without diagnosed CHD, and 1.32+/-0.83 mg/dL for persons with CHD. The odds ratio for high CHD risk in the highest quintile of OxLDL, compared with the lowest quintile and after adjusting for age, sex, race, LDL cholesterol, smoking status, and C-reactive protein, was 2.79. The conclusion set forth in the Abstract is that the odds ratio for elevated OxLDL among persons with high CHD risk before any CHD events was higher than that among persons with established CHD, and that a likely explanation is that once CHD is diagnosed, individuals are frequently treated with a statin, which is associated with lowering of LDL cholesterol and OxLDL levels. The conclusion at the end of the paper reads: "In agreggate, this study shows for the first time in the general populaton that high CHD risk before the occurrence of CHD events is associated with high levels of circulating OxLDL, even after adjustment for LDL cholesterol. Our data suggest that circulating OxLDL can be a useful marker for identifying older persons at high cardiovascular risk."

88. Hruban RH, Beschorner WE, Baumbgartner WA, Augustine SM, Ren H, Reitz BA, Hutchins GM, "Accelerated Arteriosclerosis In Heart Transplant Recipients Is Associated With A T-Lymphocyte-Mediated Endothelialitis," *Am. J. Pathol.* 1990; 137(4): 871-882, indicates that accelerated atherosclerosis can occur as soon as 3 months after heart transplantation and that it can affect recipients as young as 4 years of age (page 878).

89. Hulthe J, Fagerberg B, "Circulating oxidized LDL is associated with subclinical atherosclerosis development and inflammatory cytokines (AIR Study)," *Arterioscler Thromb Vasc Biol.* 2002 Jul 1; 22(7): 1162-1167, reports a study conducted to examine the relationship between subclinical atherosclerosis and Ox-LDL. The stated aims of the study were to investigate the relationship between clinically silent ultrasound-assessed atherosclerotic changes in the carotid and femoral arteries and Ox-LDL and to explore the relationship between Ox-LDL, C-reactive protein, and the inflammatory cytokines interleukin-6 and tumor necrosis factor-alpha. The study group (n=391) consisted of clinically healthy, 58-year-old men recruited from the general population. Ox-LDL was measured by using a specific monoclonal antibody, mAb-4E6. The results showed that Ox-LDL was related to intima-media thickness and plaque occurrence in the carotid and femoral arteries. In addition, Ox-LDL was associated with tumor necrosis factor-alpha and C-reactive protein. Circulating Ox-LDL was also associated with LDL cholesterol but not with blood pressure or smoking. When adjusting for other risk factors, both LDL cholesterol and Ox-LDL seemed to be independent predictors of plaque occurrence in the

carotid and femoral arteries (odds ratios for quintile 5 versus quintile 1 were 2.17, P=0.049 and 2.25, P=0.050, for LDL cholesterol and Ox-LDL, respectively). The conclusion set forth in the Abstract is that "Ox-LDL was associated with both subclinical atherosclerosis and inflammatory variables, supporting the concept that oxidatively modified LDL may play a major role in atherosclerosis development, although no causality can be shown in this cross-sectional study." The authors noted "It is unknown whether CRP exerts a direct effect on the atherosclerotic process or if serum CRP elevation is a phenomenon secondary to the impact of other factors" and that the results of the present study showed a positive assocation between Ox-LDL and CRP (page 1166).

90. Itabe H, Takeshima E, Iwasaki H, Kimura J, Yoshida Y, Imanaka T, Takano T, "A Monoclonal Antibody Against Oxidized Lipoprotein Recognizes Foam Cells In Atherosclerotic Lesions: Complex Formation Of Oxidized Phosphatidylcholines And Polypeptides," *J. Biol. Chem.* 1994; 269(21): 15274-15279, indicates that oxidative modification of LDL is believed to be involved in atherogenesis. It concerns a monoclonal antibody that reacts with oxidized LDL but not with MDA-modified LDL to investigate whether materials deposited in human atherosclerotic lesions are immunologically related to oxidized LDL.

91. Itabe H, Yamamoto H, Imanaka T, Shimamura K, Uchiyama H, Kimura J, Sanaka T, Hata Y, Takano T, "Sensitive Detection Of Oxidatively Modified Low Density Lipoprotein Using A Monoclonal Antibody," *J. Lipid Res.* 1996; 37: 45-53, concerns a new method said to be capable of measuring very low concentrations of oxidized LDL using a monoclonal antibody that does not react with MDA-modified LDL. The LDL fraction is separated from plasma before carrying out the assay (page 51). "It would certainly be useful if the oxidation levels in plasma could be measured without separating LDL, although further experiments are needed to elucidate a reliable assay procedure for this" (Id.).

92. Juckett MB, Balla J, Balla G, Jessurun J, Jacob HS, Vercellotti GM, "Ferritin Protects Endothelial Cells From Oxidized Low Density Lipoprotein In Vitro," *Am. J. Pathol.* 1995; 147(3): 782-789, suggests that ferritin may play a broader role in cellular defense by limiting oxidative injury in inflammatory conditions, such as atherosclerosis. Juckett et al. note that native LDL is not toxic to endothelium but oxidized LDL damages endothelium by oxidatively denaturing cellular membranes and organelles (page 782).

93. Kaplan R, Aynedjian HS, Schlondorff D, Bank N, "Renal Vasoconstriction Caused By Short-Term Cholesterol Feeding Is Corrected By Thromboxane Antagonist Or Probucol," *J. Clin. Invest.* 1990; 86: 1707-1714, reports on investigating the hypothesis that LDL oxidized in vivo is causally related to vascular tone abnormalities.

94. Keane WF, Mulcahy WS, Kasiske BL, Kim Y, O'Donnell MP, "Hyperlipidemia And Progressive Renal Disease," *Kidney Int.* 1991; 39(Suppl.): S41-S48, mentions that oxidized LDL may be an important lipoprotein pathogen participating in atherosclerosis.

95. Kolata, G, "A New Generation Of Tests To Determine Heart Trouble," *New York Times News Service,* 7 pages (Nov. 26, 1995), reports that half of the 600,000 Americans who have heart attacks each year have no symptoms beforehand and that as many as 30% of heart disease patients do not have any obvious risk factors such as high blood pressure, high cholesterol levels, diabetes, or a family history of heart disease. It also reports on new tests such as heart scans, which show plaque, and ultrafast or electron beam CT), which show calcium deposits, which are harbingers of heart disease, as well as tests for genetic and biochemical substances, such as apolipoprotein e, Lp(a), homocysteine, and fibrinogen. One scientist has focused on fibrinogen, which is said to be a clotting factor that may help precipitate a heart attack.

96. Koskinen P, Lemstrom K, Bruggeman C, Lautenschlager I, Hayry P, "Acute Cytomegalovirus Infection Induces A Subendothelial Inflammation (Endothelialitis) In The Allograft Vascular Wall. A Possible Linkage With Enhanced Allograft Arteriosclerosis," *Am. J. Pathol.* 1994; 144(1): 41-50, suggests that the virus-linked vascular wall inflammation may play a role in the immune injury towards allograft vascular structures, particularly to endothelium, and thus contribute to allograft atherosclerosis.

97. Kotani K, Maekawa M, Kanno T, Kondo A, Toda N, Manabe M, "Distribution Of Immunoreactive Malondialdehyde-Modified Low-Density Lipoprotein In Human Serum," *Biochimica et Biophysica Acta* 1994; 1215: 121-125, reports development of a "sensitive" ELISA for detection of MDA-modified LDL in human serum. A monoclonal antibody recognized not only MDA-modified LDL but also other MDA-modified proteins. MDA-modified LDL was able to be detected by using a combination of monoclonal antibody ML25 and an antibody specific for apolipoprotein B (apo B), AB16. Using this method,

measurable amounts of MDA-modified LDL were detected in the sera of 40 healthy individuals. LDL oxidized by copper was also detectable with this method. The method is said to be sensitive and specific for MDA-modified LDL and the authors state that it might be useful for investigating MDA-modified LDL in the human circulation. The monoclonal antibodies against MDA-modified LDL were made using MDA-modified LDL prepared by modification of 15% of the free amino residues (page 122). Clinical detection of MDA-modified LDL in human sera might be significant in connection with the early prediction of atherosclerosis (page 125).

98. Lee TH, Goldman L. "Serum Enzymes In The Diagnosis Of Acute Myocardial Infarction, *Annals of Internal Medicine* 1986; 105: 221-223, concerns detection of acute myocardial infarction by testing for substances such as CK-MB, depending on a number of factors (see Table 7 for authors' recommendations).

99. Libby P, Salomon RN, Payne DD, Schoen FJ, Pober JS, "Functions Of Vascular Wall Cells Related To Development Of Transplantation-Associated Coronary Arteriosclerosis," *Transplant. Proc.* 1989; 21(4): 3677-3684, reports that the development of a distinct form of coronary atherosclerosis in the arteries of the engraft heart has emerged as a major limitation to the long-term success of this therapy. A number of features are said to distinguish this lesion from the usual form of coronary atherosclerosis. This process is said to occur independent of the etiology of the recipient's original cardiac disease. The authors hypothesize that study of the accelerated disease may aid understanding of atherogenesis in general and that unraveling the basic pathobiology of these clinically important arterial diseases should lay the groundwork for rational design of selective therapeutic strategies to prevent or retard their development (page 3683).

100. Lynch SM, Morrow JD, Roberts II LJ, Frei B, "Formation Of Non-Cyclooxygenase-Derived Prostanoids ($F_2$-Isoprostanes) In Plasma And Low Density Lipoprotein Exposed To Oxidative Stress In Vitro," *J. Clin. Invest.* 1994; 93: 998-1004, notes that oxidation of LDL is a likely causal factor for atherosclerosis and that $F_2$-isoprostanes may be useful markers of LDL oxidation in vivo.

101. Mabile L, Fitoussi G, Periquet B, Schmitt A, Salvayre R, Negre-Salvayre A, "Alpha-Tocopherol And Trolox Block The Early Intracellular Events (TBARS And Calcium Rises) Elicited By Oxidized Low Density Lipoproteins In Cultured Endothelial Cells," *Free*

*Radic. Biol. Med.* 1995; 19(2): 177-187, notes that oxidized LDLs have been detected in atherosceroltic lesions and are thought to be involved in atherogenesis.

102. Major AS, Dove DE, Ishiguro H, Su YR, Brown AM, Liu L, Carter KJ, Linton MF, Fazio S, "Increased Cholesterol Efflux In Apolipoprotein AI (ApoAI)-Producing Macrophages As A Mechanism For Reduced Atherosclerosis In ApoAI((-/-)) mice," *Arterioscler Thromb Vasc Biol.* 2001 Nov; 21(11): 1790-1795, reports a study whose "data support the hypothesis that apoAI production by macrophages in the artery wall is protective against atherosclerosis. This protection is likely mediated by increased cholesterol efflux and decreased foam cell formation in vivo." (Abstract) "Apolipoprotein AI (apoAI) is a major protein component of HDL. There is a well-established inverse correlation between HDL cholesterol and/or apoAI serum levels and the risk of coronary heart disease (CHD)." (page 1790; citation omitted) "ApoAI is a major protein component of HDL. In the mouse and in humans, apoAI is made primarily by the liver and intestine. Patients and animal models with apoAI deficiency have highlighted the importance of this molecule in lipoprotein metabolism and its involvement in atherogenesis." (page 1793). "ApoE and apoAI are thought to be antiatherogenic by several mechanisms. Because enhancement of cholesterol efflux is a shared function of apoAI and apoE, we believe that these experiments emphasize the protective effect of reverse cholesterol transport in the developing atherosclerotic plaque." (page 1794)

103. Menschikowski M, Kasper M, Lattke P, Schiering A, Schiefer S, Stockinger H, Jaross W, "Secretory Group II Phospholipase A2 In Human Atherosclerotic Plaques," *Atherosclerosis* 1995; 118: 173-181, notes that because atherosclerotic plaques exhibit features similar to chronic inflammation and that during inflammation some cells produce and secrete a particular enzyme, a immunohistochemical study using monoclonal antibodies was performed to determine whether that enzyme was present in human atherosclerotic lesions. The study concluded that the enzyme was present in human atherosclerotic plaques but not in normal arteries and that the data support the view that atherosclerosis is associated with a special form of chronic inflammatory response in injured arteries.

104. McCully KS, "Chemical Pathology Of Homocysteine. I. Atherogenesis," *Ann. Clin. Lab. Sci.* 1993; 23(6): 477-493, reports on the various atherogenic properties of homocysteine.

105. Morrow JD, Awad JA, Boss HJ, Blair IA, Roberts II LJ, "Non-Cycloogenase-Derived Prostanoids ($F_2$-isoprostanes) Are Formed In Situ On Phospholipids," *Proc. Natl. Acad. Sci. USA* 1992; 89: 10721-10725, concerns the mechanisms for oxidant injury in vivo.

106. Muldoon MF et al., Ryan J et al., Oltrona L et al., and Liuzzo G et al., letters and reply by authors, "C-Reactive Protein And Serum Amyloid A Protein In Unstable Angina," *N. Engl. J. Med.* 1995; 332(6): 398-400, concerns whether C-reactive protein and amyloid A protein are markers of the activity of atherosclerosis and whether they have predictive value for patients with unstable angina. One of the letters notes the evidence that athersclerosis is an inflammatory disease and that fibrinogen has been found to be correlated with the risk of heart disease (Muldoon letter, page 398).

107. Murugesan G, Chisolm GM, Fox PL, "Oxidized Low Density Lipoprotein Inhibits The Migration Of Aortic Endothelial Cells In Vitro," *J. Cell. Biol.* 1993; 120(4): 1011-1019, notes that oxidized LDL is present in atherosclerotic lesions.

108. Neff MS, Eiser AR, Slifkin RF, Baum M, Baez A, Gupta S, Amarga E, "Patients Surviving 10 Years Of Hemodialysis," *Am. J. Med.* 1983; 74: 996-1004, notes that prolonged dialysis treatment is associated with accelerated atherogenesis.

109. Ohman EM, Armstrong PW, Christenson RH, Granger CB, Katus HA, Hamm CW, O'Hanesian MA, Wagner GS, Kleiman NS, Harrell Jr. FE, Califf RM, Topol EJ, "Cardiac Troponin T Levels For Risk Stratification In Acute Myocardial Ischemia," *N. Eng. J. Med.* 1996 335(18): 1333-1341, studied cardiac troponin T and CK-MB and concluded that the troponin T level was a powerful, independent risk marker in patients who present with acute myocardial ischemia and that it allows further stratification of risk when combined with standard measures such as electrocardiography and the CK-MB level.

110. O'Marcaigh AS, Jacobson RM, "Estimating The Predictive Value Of A Diagnostic Test. How To Prevent Misleading Or Confusing Results," *Clin. Ped.* 1993; 32(8): 485-491, discusses specificity, sensitivity, and positive and negative predictive values of a test, e.g., a clinical diagnostic test.

111. Palinski W, Rosenfeld ME, Ylä-Herttuala S, Gurtner GC, Socher SS, Butler SW, Parthasarathy S, Carew TE, Steinberg D, Witztum JL, "Low Density Lipoprotein Undergoes Oxidative Modification In Vivo," *Proc. Natl. Acad. Sci. USA* 1989; 86: 1372-1376,

uses monoclonal antibodies to detect, e.g., MDA-modified LDL and 4-HNE-low density lipoprotein (page 1372). One of the antibodies was "specifically directed to the MDA-lysine epitope, recognizing it on any of a variety of different proteins" (page 1373). "[O]xidation of LDL even without any added MDA generates MDA-lysine adducts, presumably the result of the peroxidation of polyunsaturated fatty acids" (page 1374). "Three lines of evidence" suggest that LDL undergoes oxidative modification in vivo, that it accumulates in aortic lesions, and that it may be a source of autoantibody production even in normal animals and normal human subjects (page 1376).

112. Palinski W, Yla-Herttuala S, Rosenfeld ME, Butler SW, Socher SA, Parthasarathy S, Curtiss LK, Witztum JL, "Antisera And Monoclonal Antibodies Specific For Epitopes Generated During Oxidative Modification Of Low Density Lipoprotein," *Arteriosclerosis* 1990; 10(3): 325-335, notes that an increasing number of observations suggest that oxidative modification of LDL occurs in vivo and plays an important role in atherogenesis. The article reports on polyclonal and monoclonal antibodies that was developed using MDA-modified LDL, copper-oxidized LDL, and 4-hydroxynonenal-LDL. The antibodies are said to be specific against three different epitopes found in oxidatively modified LDL, and one of the monoclonal antibodies is said to be specific MDA-lysine. The degree of MDA modification in the MDA-modified LDL employed averaged 77% of the lysine residues for a typical preparation (page 326). The authors indicate that these antibodies should prove useful in studying the role of oxidatively modified lipoproteins as well as other oxidatively modified proteins in atherogenesis.

113. Parthasarathy S, Wieland E, Steinberg D, "A Role For Endothelial Cell Lipoxygenase In The Oxidative Modification Of Low Density Lipoprotein," *Proc. Nat. Acad. Sci. USA* 1989; 86: 1046-1050, notes that oxidative modification of LDL has been implicated as a factor in the generation of macrophage-derived foam cells in vitro and in vivo and that one of the early events in atherosclerosis is the accumulation of cholesterol-laden foam cells in the subendothelial space.

114. Penn MS, Chisolm GM, "Oxidized lipoproteins, altered cell function and atherosclerosis," *Atherosclerosis* 1994; 108(Suppl.): S21-S29, notes that a correlation between atherogenesis and lipoprotein oxidation has been suggested and that there are theories that lipoprotein oxidation is causally related to arterial disease.

115. Pocock SJ, *Clinical Trials. A Practical Approach.* Chapter 14: "Further Aspects Of Data Analysis," pages 211-233, John Wiley & Sons, 1993, concerns interpretation of clinical data.

116. Rasmussen O, Thomsen C, Ingerslev J, Hermansen K, "Decrease Of Von Willebrand Factor Levels After A High-Monounsaturated Fat Diet In Non-Insulin-Dependent Diabetic Subjects," *Metabolism* 1994; 43(11): 1406-1409, notes that the major cause of disability and mortality in non-insulin-dependent diabetes is cardiovascular disease, that factors such as hypertension and lipoprotein and hemostatic abnormalities all increase the risk of vascular disease, and that Von Willebrand factor is known to be increased in diabetes, particularly in the presence of vascular complications, and consequently serves as a risk predictor. The authors note that fibrinogen, a protein belonging to the group of acute phase reactants, is regarded as an established risk factor for stroke and ischemic heart disease (page 1408).

117. Ravalli S, Marboe CC, D'Agati VD, Michler RE, Sigal E, Cannon PJ, "Immunohistochemical Demonstration Of 15-Lipoxygenase In Transplant Coronary Artery Disease," *Arterioscler. Thromb. Vasc. Biol.* 1995; 15(3): 340-348, notes that 15-lipoxygenase has been implicated in the oxidative modification of LDL and reports on a study made to investigate whether that enzyme was also present in the accelerated form of coronary artery disease that can complicate cardiac transplantation. The study involved the use of monoclonal and polyclonal antibodies. The authors also note that increasing evidence has accumulated that the oxidative modification of LDL may play a role in the pathogenesis of atherosclerosis.

118. Reade V, Tailleux A, Reade R, Harduin P, Cachera C, Tacquet A, Fruchart JC, Fievet C, "Expression Of Apolipoprotein B Epitopes In Low Density Lipoproteins Of Hemodialyzed Patients," *Kidney Int.* 1993; 44: 1360-1365, notes that elevated plasma levels of LDL are associated with atherogenesis and reports investigating the accessibility of monoclonal antibodies to various epitopes on LDL-apo B 100 and the possible relationship between accessibility of those epitopes and the composition of LDL isolated from hemodialyzed patients.

119. Reverter JC, Escolar G, Sanz C, Cases A, Villamor N, Nieuwenhuis HK, Lopez J, Ordinas A, "Platelet Activation During Hemodialysis Measured Through Exposure Of P-Selectin: Analysis By Flow Cytometric And Ultrastructural Techniques," *J. Lab. Clin. Med.* 1994; 124(1): 79-85, notes that the detection of certain proteins exposed on the surface of stimulated platelets (e.g., P-selectin) is seen as a useful approach to determine early stages of

clinical thrombosis and that use of monoclonal antibodies directed against activation-dependent antigens and flow cytometry is regarded as a promising approach for detection of the early stages of thrombosis.

120. Ridker PM, Glynn, RJ, Hennekens, CH, "C-Reactive Protein Adds To The Predictive Value Of Total And HDL Cholesterol In Determining Risk Of First Myocardial Infarction," *Circulation*, 1998; 97:2007-2011, notes that "C-reactive protein (CRP) is a sensitive marker of inflammation, and [that] elevated levels have been associated with future risk of myocardial infarction (MI) ... [but that] whether measurement of CRP adds to the predictive value of total cholesterol (TC) and HDL cholesterol (HDL-C) in determining risk is uncertain" and concludes that "[i]n prospective data from a large cohort of apparently healthy men, baseline CRP level added to the predictive value of lipid parameters in determining risk of first MI." (Abstract) Ridker et al. also note that certain "data demonstrate that CRP is a marker of cardiovascular risk not only among those with stable and unstable angina, the elderly, and selected high-risk patients but also among individuals with no current evidence of cardiovascular disease" (page 2007). The legend for Figure 2 reads: "Relative risks of first MI among apparently healthy men associated with high (>223 mg/dL), middle (191 to 223 mg/dL), and low (<191 mg/dL) tertiles of TC and high (>1.69 mg/L), middle (0.72 to 1.69 mg/L), and low (<0.72 mg/L) tertiles of CRP." The legend for Figure 3 reads: "Relative risks of first MI among apparently healthy men associated with high (>5.01), middle (3.78 to 5.01), and low (<3.78) tertiles of the TC:HDL-C ratio and high (>1.69 mg/L), middle (0.72 to 1.69 mg/L), and low (<0.72 mg/L) tertiles of CRP." In the Discussion section, Ridker et al. note: "In these prospective data deriving from a large cohort of apparently healthy men, baseline CRP level added to the predictive value of TC and HDL-C in determining risk of first MI. Indeed, interactive models evaluating elevations of CRP and lipids raise the possibility that the joint effects of both risk factors may be slightly greater than the product of the individual effects of each risk factor considered separately. Moreover, baseline level of CRP is a predictor of risk of first MI for men at low as well as high risk as determined by their lipid profiles." They also note at page 2011 that "[t]he present data raise the possibility that assessment of CRP may provide a method of determining risk of future MI among apparently low-risk individuals, including nonsmokers," that "up to half of all MIs in the United States occur among individuals with moderate to low risk as determined by assessment of TC and HDL-C levels" (citation omitted),

and that "[t]he present data raise the possibility that assessment of CRP may provide a method of determining risk of future MI among apparently low-risk individuals, including non-smokers."

121. Ridker PM, Buring JE, Shih J, Matias M, Hennekens CH, "Prospective Study Of C-Reactive Protein And The Risk Of Future Cardiovascular Events In Stable And Unstable Angina," *Circulation* 1998; 98:731–733, notes that "C-reactive protein (CRP) is a marker for inflammation that appears to predict cardiovascular events among apparently healthy men" and that "CRP adds to the predictive value of total and HDL cholesterol such that the risk of future MI for men with elevated levels of CRP and hyperlipidemia appears to be greater than the product of the risks associated with either abnormality alone" but that "[i]n women, prospective data evaluating CRP are sparse" (page 731). "These prospective data indicate that baseline CRP concentration is an independent risk factor for cardiovascular disease among apparently healthy middle-aged women. Moreover, in these data, the predictive value of models that include CRP is significantly better than those limited to usual risk factors. Finally, these data indicate that CRP predicts vascular events even among low-risk subgroups of women with no readily apparent markers for disease." (pages 732-733) "These data support the hypothesis that low-grade inflammation is a marker for subsequent cardiovascular disease. Whether CRP has direct vascular or prothrombotic effects, reflects underlying endothelial dysfunction due to prevalent atherosclerosis, leads to increased lipid peroxidation, or is simply a marker resulting from an as yet undetermined environmental and/or infectious stimulus remains to be elucidated." (Id.)

122. Rose EA, Smith CR, Petrossian GA, Barr ML, Reemtsma K, "Humoral Immune Responses After Cardiac Transplantation: Correlation With Fatal Rejection And Graft Atherosclerosis," *Surgery* 1989; 106(2): 203-208, notes that the long-term outlook for heart transplant patients is limited by rejection and graft atherosclerosis.

123. Rosenfeld ME, Palinski W, Yla-Herttuala, Butler S, Witztum JL, "Distribution Of Oxidation Specific Lipid-Protein Adducts And Apolipoprotein B In Atherosclerotic Lesions Of Varying Severity From WHHL Rabbits," *Arteriosclerosis* 1990; 10(3): 336-349, used the antibodies referenced in Palinski et al., *Arteriosclerosis* 1990; 10(3): 325-335 (discussed herein) to immunostain atherosclerotic lesions of varying severity from Watanabe heritable hyperlipidemic rabbits. "Although the site(s) at which the oxidation process occurs have yet to be determined, the cell-associated staining patterns we observed suggest that

the oxidation of LDL may be mediated by the cells within atherosclerotic lesions and that the resulting oxidized LDL may be taken up by the cells and may be the ultimate source of the lipids that accumulate in atherosclerotic lesions" (page 348).

124. Ross R, "The Pathogenesis Of Atherosclerosis: A Perspective For The 1990s," *Nature* 1993; 362: 801-809, is a review article. "Atherosclerosis, the principal cause of heart attack, stroke and gangrene of the extremities, is responsible for 50% of all mortality in the USA, Europe and Japan. The lesions result from an excessive, inflammatory-fibroproliferative response to various forms of insult to the endothelium and smooth muscle of the artery wall." (Abstract) It discusses, among other things, the role of oxidized LDL in the disease. It notes that recent data have shown that most of the sudden deaths from acute myocardial infarction are due to ruptures or fissures in the plaques, resulting in hemorrhaging into the plaque, thrombosis, and occlusion of the artery.

125. Salonen JT, Yla-Herttuala S, Yamamoto R, Butler S, Korpela H, Salonen R, Nyyssonen K, Palinski W, Witztum JL, "Autoantibody Against Oxidised LDL And Progression Of Carotid Atherosclerosis," *Lancet* 1992; 339(8798): 883-887, notes that oxidative modification of LDL renders it immunogenic and that autoantibodies to epitopes of oxidized LDL, such as MDA-lysine, are found in serum and recognize material in atheromatous tissue. The authors compared the titer of autoantibodies to MDA-modified LDL and native LDL in baseline human serum samples from thirty Finish men who had accelerated two-year progression of carotid atherosclerosis and concluded that the titer of autoantibodies to MDA-modified LDL was an independent predictor of the progression of carotid atherosclerosis in those Finnish men. The authors also stated that their data provide further support for a role of oxidatively modified LDL in atherogenesis. The authors did note a qualification to their study, namely, that the antibodies for which the titer was determined could recognize MDA-lysine epitopes on other MDA-modified proteins in either serum or tissue (page 886).

126. Sasavage N, "Predicting Coronary Artery Disease. New Markers Could Identify Patients At Risk," *Clin. Lab. News,* March 1998; pages 6-7, suggests that oxidation of low density lipoproteins may render it more atherogenic, that detection of oxidized LDL species faces some technical difficulties, and indicates that coronary artery disease appears to be a multifactorial disease. It notes that some researchers believe that a low-level inflammatory state induced by infectious agents (e.g., cytomeglovirus) may be a trigger of plaque formation and that

serum markers for adhesion molecules, lipid levels, and antibody titres – which detect vascular inflammation – could be useful predictive markers for people at risk for acute coronary syndromes. It also states that those who work in this area agree that development of a new generation of biochemical markers will allow clinicians to better assess patient risk and intervene with treatments to avoid adverse outcomes.

127. Savenkova ML, Mueller DM, Heinecke JW, "Tyrosyl Radical Generated By Myeloperoxidase Is A Physiological Catalyst For The Initiation Of Lipid Peroxidation In Low Density Lipoprotein," *J. Biol. Chem.* 1994; 269(32): 20394-20400, concludes that the links between myeloperoxidase, which is expressed in human atherosclerotic lesions, and LDL oxidation in vitro support the hypothesis that the heme enzyme may promote lipoprotein oxidation in vivo and therefore may be a pivotal agent in the development of atherosclerotic lesions.

128. Schaffner T, Taylor K, Bartucci EJ, Fischer-Dzoga K, Beeson JH, Glagov S, Wissler RW, "Arterial Foam Cells With Distinctive Immunomorphologic And Histochemical Features Of Macrophages," *Am. J. Pathol.* 1980; 100(1): 57-80, reports on a study of fat-filled foam cells in diet-induced experimental arterial intimal plaques in rabbits and monkeys.

129. Schonbeck U, Gerdes N, Varo N, Reynolds RS, Horton DB, Bavendiek U, Robbie L, Ganz P, Kinlay S, Libby P, "Oxidized low-density lipoprotein augments and 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors limit CD40 and CD40L expression in human vascular cells," *Circulation* 2002; 106(23):2888-2893, concerns a "study [that] analyzed whether oxidized low-density lipoprotein (oxLDL) induces CD40/CD40L expression on cells implicated in atherogenesis and whether statins affect their expression in vitro as well as the expression of soluble CD40L (sCD40L) in vivo." (Abstract) "Atherosclerosis bears many hallmarks of chronic inflammation..." (page 2888). The conclusions read as follows: "OxLDL may promote expression of CD40 and CD40L in human atheroma. Statins may limit the expression of the CD40 receptor/ligand dyad in two ways, directly as well as through diminished lipoprotein levels. Thus, reduced CD40 signaling may account for some of the statins' antiinflammatory action." (Id.) In the Results section, Schonbeck et al. note that "[o]xidatively modified LDL (oxLDL) concentration-dependently enhanced the faint constitutive expression of CD40 and CD40L protein in human vascular ECs ... and MØ .... Native LDL also induced expression of the receptor ... although to a lesser extent. Furthermore, oxLDL concentration-

dependently augmented the expression of CD40 and CD40L mRNA in human vascular EC ..." (page 2890). "Plasma concentrations of C-reactive protein were lower in the statin-treated group, although the difference did not achieve statistical significance" (page 2891).

130. Shacter E, "Quantification And Significance Of Protein Oxidation In Biological Samples," *Drug Metab Rev.* 2000 Aug-Nov; 32(3-4): 307-26, concerns protein oxidation. "Protein oxidation is defined here as the covalent modification of a protein induced either directly by reactive oxygen species or indirectly by reaction with secondary by-products of oxidative stress. Oxidative modification of proteins can be induced experimentally by a wide array of prooxidant agents and occurs in vivo during aging and in certain disease conditions. Oxidative changes to proteins can lead to diverse functional consequences, such as inhibition of enzymatic and binding activities, increased susceptibility to aggregation and proteolysis, increased or decreased uptake by cells, and altered immunogenicity. There are numerous types of protein oxidative modification and these can be measured with a variety of methods. Protein oxidation serves as a useful marker for assessing oxidative stress in vivo." (page 308) Table 1 lists various mechanisms that induce protein oxidation and the amino acids involved, and lipid peroxidation adducts (e.g., malondialdehyde (MDA)) are listed (page 309). "Indirect oxidative modification of protein amino acyl side chains occurs through the formation of adducts with products of oxidatively modified lipids, amino acids, sugars, and glutathione. For example, lipid peroxidation breakdown products such as hydroxynonenal (HNE), malondialdehyde (MDA), and acrolein bind covalently to Lys, His, and Cys residues, leading to the addition of aldehyde moieties to the protein. (page 310; citations omitted) "Plasma low-density lipoprotein (LDL) has been demonstrated to undergo several different types of oxidative modification. Exposure of LDL to $Cu^{+}$ causes oxidation of the LDL protein, leading to the formation of carbonyl groups, aggregation, and increased cellular uptake by tissue macrophages through the scavenger receptor. Importantly, oxidatively modified LDL has been found in atherosclerotic tissues by several groups, lending strong support for the idea that oxidation of LDL may play a significant role in the etiology of atherosclerosis." (page 311; citations omitted; see also Table 3 on page 312) "Importantly, the nature of the protein modification can give significant information as to the type of oxidant involved in the oxidation process. For example, chlorotyrosyl moieties and amino acyl adducts on lysine residues are probably specific markers of oxidation by HOCl and, hence, reflect neutrophil and/or monocyte involvement in the oxidative stress. Both of these

types of oxidation products have been found in human atherosclerotic lesions...." (page 316; citations omtted)

131. Shultz EK, "Clinical Interpretation Of Laboratory Procedures," Chapter 14 in *Teitz, Fundamentals of Clinical Chemistry*, Burtis CA, Ashwood ER (eds.), 4th edition 1996, W.B.Saunders Company, pages 192-199, discusses sensitivity and specificity of tests, e.g., diagnostic tests, as well as ROC curve analysis.

132. Schulz T, Schiffl H, Scheithe R, Hrboticky N, Lorenz R, "Preserved Antioxidative Defense Of Lipoproteins In Renal Failure And During Hemodialysis," *Am. J. Kidney Dis.* 1995; 25(4): 564-571, notes that LDL has been shown to be much more atherogenic after oxidative modification and that the severity of coronary atherosclerosis has been correlated to the susceptibility of LDL to oxidation. It also notes that accelerated atherosclerosis and the consequences are a major cause of morbidity and mortality in long-term hemodialysis patients.

133. Selwyn AP, Kinlay S, Libby P, Ganz P, "Atherogenic Lipids, Vascular Dysfunction, And Clinical Signs Of Ischemic Heart Disease," *Circulation* 1997; 95(1): 5-7, notes that low levels of oxidized LDL (from 1 to 10 micrograms/mL, which is 0.1 to 1 mg/dL) appear to encourage cell integrity and that physiological and pathological concentrations (10 to 100 micrograms/mL, which is 1 to 10 mg/dL) can trigger all the listed dysfunctions that are characteristic in experimental and clinical atherosclerosis (pages 5-6). It also notes that there is limited evidence that increased levels of oxidized LDL or greater susceptibility of LDL to oxidation is related to the severity of coronary atherosclerosis (page 6). It further notes that lipid lowering appears to stabilize atheroma in the long term, improves endothelium-dependent vasomotion over months, and results in a reduction in clinical signs of risk in coronary heart disease (Id.). "Treatment of atherogenic lipids with other risk factors must be further refined and may well become the cornerstone for effective management of angina, unstable syndromes, and ischemia in addition to the control of important outcomes such as myocardial infarction and coronary death (page 7).

134. Sparrow CP, Olszewski J, "Cellular Oxidative Modification Of Low Density Lipoprotein Does Not Require Lipoxygenases," *Proc. Nat. Acad. Sci. USA* 1992; 89: 128-131, notes that there is evidence that an important part of the pathogenesis of atherosclerosis is the oxidative modification of LDL.

135. Sparrow CP, Partharasathy S, Leake DS, Steinberg D, "Enzymatic Modification Of Low Density Lipoprotein By Purified Lipoxygenase Plus Phospholipase-$A_2$ Mimic Cell-Mediated Oxidative Modification," *J. Lipid Res.* 1988; 29: 745-753, notes that LDL can be oxidatively modified by cultured endothelial cells or by copper ions, resulting in increased macrophage uptake of the LDL.

136. Steinberg D, Witztum JL, "Lipoproteins And Atherogenesis: Current Concepts," *J. Am. Med. Assoc.* 1990; 264(23): 3047-3052, discusses oxidized LDL at page 3048 and notes that oxidized LDL may contribute to atherogenesis above and beyond its direct contribution to macrophage lipid accumulation.

137. Steinberg D, "Clinical Trials Of Antioxidants In Atherosclerosis: Are We Doing The Right Thing?" *Lancet* 1995; 346: 36-38, notes that the hypothesis that oxidative modification of low density lipoprotein contributes to the progression of atherosclerosis is supported by an impressive body of in vitro findings and by persuasive results in animal models of atherosclerosis. At page 37, the article proposes more emphasis on certain clinical intervention trials and states that one possibility is the use of ultrasound to follow changes in intima-thickness in a common carotid artery. "This technique has been validated as a measurement that correlates with changes in the coronary arteries but it appears to deal with an earlier stage of the disease than that which determines clinical events" (citations omitted) (Id.).

138. Steinberg D, "Lewis A. Conner Memorial Lecture. Oxidative Modification Of LDL And Atherogenesis," *Circulation* 1997; 95: 1062-1071, is a review article. It notes that deaths from coronary heart disease continue to outnumber deaths from any other single cause in the United States (page 1062); that oxidation of LDL is "an incredibly complex process," that there is no unique LDL particle corresponding to "oxidized LDL" and that there is a broad spectrum of oxidized LDLs; that the rate of lesion progression is a function of LDL concentration, of the rate of LDL oxidation, and of other variables (page 1064); and that despite 15 years of intensive research, many questions remain unanswered regarding OxLDL (page 1068).

139. Steinbrecher UP, Parthasarathy S, Leake DS, Witztum JL, Steinberg D, "Modification Of Low Density Lipoprotein By Endothelial Cells Involves Lipid Peroxidation And Degradation Of Low Density Lipoprotein Phospholipids," *Proc. Nat. Acad. Sci. USA* 1984; 81: 3883-3887, reports that LDL incubated with cultured endothelial cells from rabbit aorta or

human umbilical vein is altered in several ways and that antioxidants completely prevented these changes.

140. Steinbrecher UP, "Oxidation Of Low Density Lipoprotein Results In Derivatization Of Lysine Residues Of Apolipoprotein B By Lipid Peroxide Decomposition Products," *J. Biol. Chem.* 1987; 262(8): 3603-3608, notes that modification of LDL by oxidation has been shown to permit recognition by the acetyl-LDL receptor of macrophages and that data suggest the oxidation of LDL is accompanied by derivatization of lysine ϵ-amino groups by lipid products and that these adducts may be important in the interaction of oxidized LDL with the acetyl-LDL receptor.

141. Steinbrecher UP, Lougheed M, "Scavenger Receptor-Independent Stimulation Of Cholesterol Esterification In Macrophages By Low Density Lipoprotein Extracted From Human Aortic Intima," *Arterioscler. Thromb.* 1992; 12(5): 608-625, notes the evidence that modification of LDL in the artery wall may contribute to atherogenesis and that the objectives of the study reported were to isolate LDL from lesion-free intima as well as from lesions using minimally perturbing methods, to define the extent of oxidation as well as other possible modifications, and to determine the mechanism by which aortic LDL can stimulate cholesterol esterification in cultured macrophages. A monoclonal antibody specific for malondiadehyde-lysine was used. Figure 5 shows the reactivity of aldehyde-specific antisera with aortic LDL.

142. Sutherland WH, Walker RJ, Ball MJ, Stapley SA, Robertson MC, "Oxidation Of Low Density Lipoproteins From Patients With Renal Failure Or Renal Transplants," *Kidney Int.* 1995; 48: 227-236, notes that patients with chronic renal failure have a substantially increased risk of death from cardiovascular disease compared with age-matched individuals from the general population (page 227) and that recent evidence suggests that oxidation of LDL in vitro may not necessarily parallel in vivo oxidation of the lipoprotein measured as circulating levels of autoantibodies to oxidized LDL (page 235). The study reported provides evidence that LDL from women with renal transplants is abnormally susceptible to oxidation in vitro and this may possibly increase their risk of future atherosclerotic disease (page 235), and the authors indicate that measurement of autoantibodies against oxidized LDL is required to confirm that oxidation of LDL in vivo may also be increased in these women (Id.).

143. Tamai O, Matsuoka H, Itabe H, Wada Y, Kohno K, Imaizumi T, "Single LDL Apheresis Improves Endothelium-Dependent Vasodilation In Hypercholesterolemic Humans," *Circulation* 1997; 95(1): 76-82, notes that it has been suggested that oxidized LDL plays a role in the development of atherosclerosis. The study reported concluded that even a single session of LDL apheresis with the reduction of total LDL and oxidized LDL improved endothelial function and indicated that the results suggest that total LDL and/or oxidized LDL may directly impair endothelial function in the human forearm vessel. Blood samples from the patients were ultracentrifuged and tested for oxidized LDL using monoclonal antibody FOH1a/DLH3 in a sandwich ELISA, which method is said to be described in Itabe et al., *J. Biol. Chem.* 1994; 269(21): 15274-15279, above, and Itabe et al., *J. Lipid Res.* 1996; 37: 45-53, above.

144. Tanaka H, Sukhova GK, Swanson SJ, Cybulsky MI, Schoen FJ, Libby P, "Endothelial And Smooth Muscle Cells Express Leukocyte Adhesion Molecules Heterogeneously During Acute Rejection Of Rabbit Cardiac Allografts," *Am. J. Pathol.* 1994; 144(5): 938-951, notes that rejection and development of chronic vascular disease continue to limit survival of recipients of cardiac allografts.

145. Trachtman H, Schwob N, Maesaka J, Valderrama E, "Dietary Vitamin E Supplementation Ameliorates Renal Injury In Chronic Puromycin Aminonucleoside Nephropathy," *J. Am. Soc. Nephrol.* 1995; 5(10): 1811-1819, reports that the only demonstrable effect of Vitamin E supplementation in normal rats was a reduction in renal cortical malondialdehyde contact. It was concluded that administration of a diet that is modestly enriched in Vitamin E protects against the development of progressive renal damage in chronic puromycin aminonucleoside nephropathy.

146. Tuzcu EM, Hobbs RE, Rincon G, Bott-Silverman C, De Franco AC, Robinson K, McCarthy PM, Stewart RW, Guyer S, Nissen SE, "Occult And Frequent Transmission Of Atherosclerotic Coronary Disease With Cardiac Transplantation, Insights From Intravascular Ultrasound," *Circulation* 1995; 91(6): 1706-1713, notes that transplant coronary artery disease is a major cause of morbidity and mortality after cardiac transplantation but that only limited data exist regarding the potential contribution of coronary atherosclerosis in the donor heart to cardiac-allograft vasculopathy. It was concluded that coronary atherosclerosis is frequently but inadvertently transmitted by means of cardiac transplantation from the donor to

the recipient. "This study also highlights the limitations of standard coronary arteriography for detecting early transplant coronary disease" (page 1711).

147. Uchida K, Kanematsu M, Sakai K, Matsuda T, Hattori N, Mizuno Y, Suzuki D, Miyata T, Noguchi N, Niki E, Osawa T, "Protein-Bound Acrolein: Potential Markers For Oxidative Stress," *Proc. Natl. Acad. Sci. USA* 1998; 95: 4882-4887, concluded that the protein-bound acrolein represents potential markers of oxidative stress and long-term damage to protein in aging, atherosclerosis, and diabetes. A monoclonal antibody was used to verify the presence of the protein-bound acrolein in vivo.

148. Van de Werf F, "Cardiac Troponins In Acute Coronary Syndromes," *N. Eng. J. Med.* 1996; 335(18): 1388-1389, states that the results of several studies convincingly demonstrate the value of cardiac troponin levels for early stratification of risk in patients with acute coronary syndromes and that it is very likely that routinely measuring cardiac troponins in serum when patients with acute coronary syndromes are admitted to the hospital will provide a more sensitive and specific identification of those at increased risk for cardiac events, including death.

149. Varo N, de Lemos JA, Libby P, Morrow DA, Murphy SA, Nuzzo R, Gibson CM, Cannon CP, Braunwald E, Schonbeck U, "Soluble CD40L: Risk Prediction After Acute Coronary Syndromes," *Circulation* 2003; 108(9):1049-1052, noted that "Elevated plasma concentrations of soluble CD40 ligand (sCD40L) indicate increased risk for future cardiovascular events in apparently healthy women" and that the purpose of the study was to test "the hypothesis that plasma sCD40L, alone or in combination with troponin (cTnI) or C-reactive protein (CRP), may identify patients with acute coronary syndromes at heightened risk for recurrent cardiac events." (Abstract) Varo et al. concluded that "[e]levated plasma levels of sCD40L identify patients with acute coronary syndromes at heightened risk of death and recurrent MI independent of other predictive variables, including cTnI and CRP" and that "combined assessment of sCD40L with cTnI complements prognostic information for death and MI." (Id.) Varo et al. noted that "sCD40L provided better risk prediction than CRP in accord with recognition that CRP, an established inflammatory marker, only weakly predicts recurrent MI [myocardial infarction]" and stated that "[f]uture studies using larger cohorts will be needed to validate the clinical use of sCD40L independently or in combination with other markers in the prediction of cardiovascular events after ACS [acute coronary syndromes]" (pages 1051-1052).

150. Wentworth P Jr, Nieva J, Takeuchi C, Galve R, Wentworth AD, Dilley RB, DeLaria GA, Saven A, Babior BM, Janda KD, Eschenmoser A, Lerner RA, "Evidence for ozone formation in human atherosclerotic arteries," *Science* 2003; 302(5647): 1053-1056, reports evidence for the production of ozone in human disease, including that signature products unique to cholesterol ozonolysis are present within atherosclerotic tissue at the time of carotid endarterectomy, suggesting that ozone production occurs during lesion development, and that advanced atherosclerotic plaques generate ozone when the leukocytes within the diseased arteries are activated in vitro. Wentworth et al. believe the steroids produced by cholesterol ozonolysis cause effects that are critical to the pathogenesis of atherosclerosis, including cytotoxicity, lipid-loading in macrophages, and deformation of the apolipoprotein B-100 secondary structure. "The results presented here suggest that the endogenous production of ozone may be a contributory factor in atherosclerosis and may link the otherwise seemingly independent factors of cholesterol accumulation and oxidation, inflammation, and cellular damage that contribute to the pathogenesis of this disease" (page 1056).

151. Ylä-Herttuala S, Palinski W, Rosenfeld ME, Parthasarathy S, Carew TE, Butler S, Witztum JL, Steinberg D, "Evidence For The Presence Of Oxidatively Modified Low Density Lipoprotein In Atherosclerotic Lesions Of Rabbit And Man," *J. Clin. Invest.* 1989 October; 84: 1086-1095 discusses "evidence" that low density lipoproteins gently extracted from human and rabbit atherosclerotic lesions greatly resembles LDL that has been oxidatively modified in vitro. "It is unlikely that oxidative modification of LDL generates a single, reproducible form of modified LDL. More likely the oxidized LDL is a heterogeneous mixture of particles containing molecules that have been modified to different degrees and may even differ quantitatively. During the oxidative degradation of polyunsaturated fatty acids, a variety of reactive aldehyde products are formed .... Malondialdehyde (MDA) and 4-hydroxynonenal (4-HNE) are two examples of such products ..." (page 1086). Monoclonal antibodies specific for apo-B were used (page 1088, section entitled "Antibodies").

152. Zaidi S, Pandey RN, Kidwai AM, Murti CRK, "A Rapid Method For Preparation Of Sarcolemma From Frog Leg Skeletal Muscle," *Chemical Abstracts* 1982 June 7; 96(23): 196091e, concerns a preparation containing cholesterol.

153. Zawadzki Z, Milne RW, Marcel YL. "An Immunochemical Marker Of Low Density Lipoprotein Oxidation," *J. Lipid Res.* 1989; 30: 885-891, concerns the use of

monoclonal antibodies to study changes in apo B immunoreactivity during copper ion-mediated oxidation of human low density lipoprotein (page 885). The changes in immunoreactivity during such oxidation are similar to those observed upon LDL aging. (Id.). The authors state they were interested in finding an immunochemical marker of LDL oxidation, i.e., an apo B epitope whose expression was specifically and significantly altered upon oxidation (Id.) and indicate that they believe they have found a "candidate marker for the apo B modification accompanying LDL oxidation, in vitro as well as in vivo" (page 890).

154. Zhao B, Dierichs R, Harrach-Ruprecht B, Winterhorff H, "Oxidized LDL Induces Serotonin Release From Blood Platelets," *Am. J. Hematol.* 1995; 48: 285-287, notes that oxidized LDL has been detected in vivo and considered an important substance promoting atherogenesis by damaging vascular endothelium, being deposited in atherosclerotic plaques, promoting foam cell formation, and stimulating platelets.

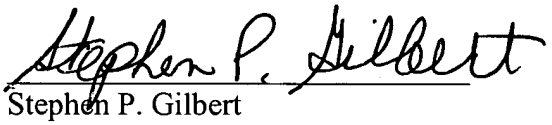
155. Zwaginga JJ, Koomans HA, Sixma JJ, Rabelink TJ, "Thrombus Formation And Platelet-Vessel Wall Interaction In The Nephrotic Syndrome Under Flow Conditions," J. Clin. Invest. 1994; 93: 204-211, notes that increased platelet adhesion, aggregate formation, and coagulation at injured vessel walls have been proposed as important mechanisms in the development of thrombosis and atherosclerosis. The results suggest that hyperfibrinogenemia may be a major thrombotic risk factor in nephrosis by inducing more fibrin depositions (page 204).

156. Zweig MH, Broste SK, Reinhart RA, "ROC Curve Analysis: An Example Showing The Relationships Among Serum Lipid And Apolipoprotein Concentrations In Identifying Patients With Coronory Artery Disease," *Clin. Chem.* 1992; 38(8): 1425-1428, discusses ROC curves and their advantages and examines the possible use of tests involving various parameters (e.g., cholesterol level, apo B level, HDL cholesterol level) to predict coronary artery disease. "One useful quantitative measure of accuracy is the area under the [ROC] curve [citing Swets JA. "Measuring The Accuracy Of Diagnostic Systems." *Science* 1988; 240: 1285-1293]. The area of interest varies from 1.0, which corresponds to perfect discrimination, to 0.5, where no discrimination exists. Swets [the cited document] suggests the following guidelines for interpretation of this area: 0.5-0.7, rather low accuracy; 0.7-0.9, accuracies useful for some purposes; and >0.9, rather high accuracy.

* * *

Documents 19, 20, 22, 27, 28, 32, 33, 35, 41, 68, 83, 84, 85, 86, 87, 89, 120, 121, and 149 are believed to be among the most relevant, documents 3, 5, 7, 8, 9, 18, 21, 26, 37, 72, 74, 76, 77, 78, 80, 81, 97, 102, 103, 106, 129, and 130 are believed to be of somewhat lesser relevance, and the remaining documents are believed to be of still lesser relevance. However, the Examiner is asked to independently review and consider all of the documents listed above before issuance of the first Office Action. The Examiner is also asked to initial and return the PTO-1449 forms to evidence such consideration.

Respectfully submitted,



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